Modelling spontaneous propagating waves in the early retina

Bruno Cessac, Dora Matzakos-Karvouniari, Lionel Gil

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Dora Matzakos-Karvouniari, LJAD, UCA
Lionel Gil, INPHYNI, UCA
Bruno Cessac, Biovision, Inria

Inria informatiques mathématiques
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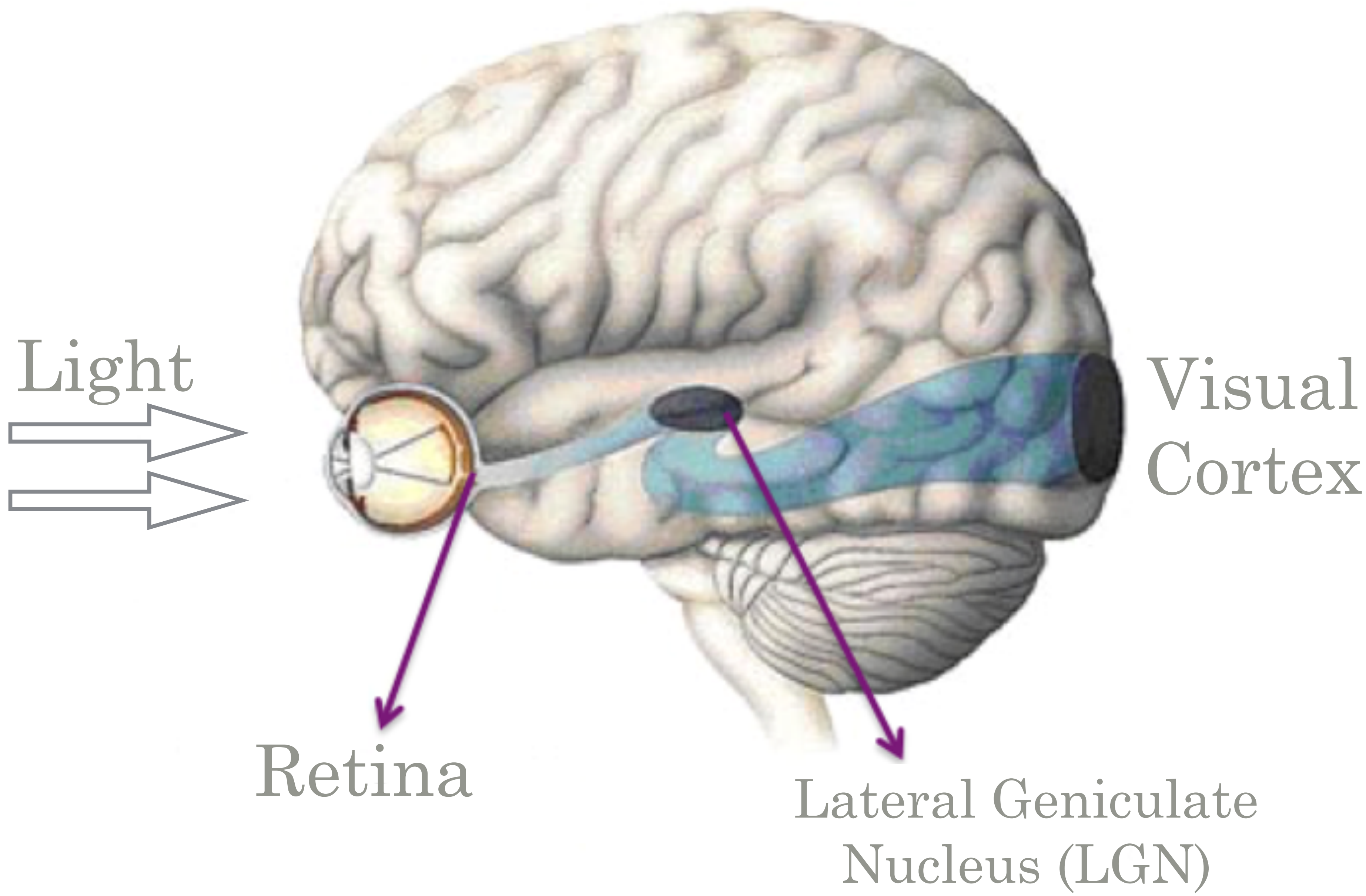
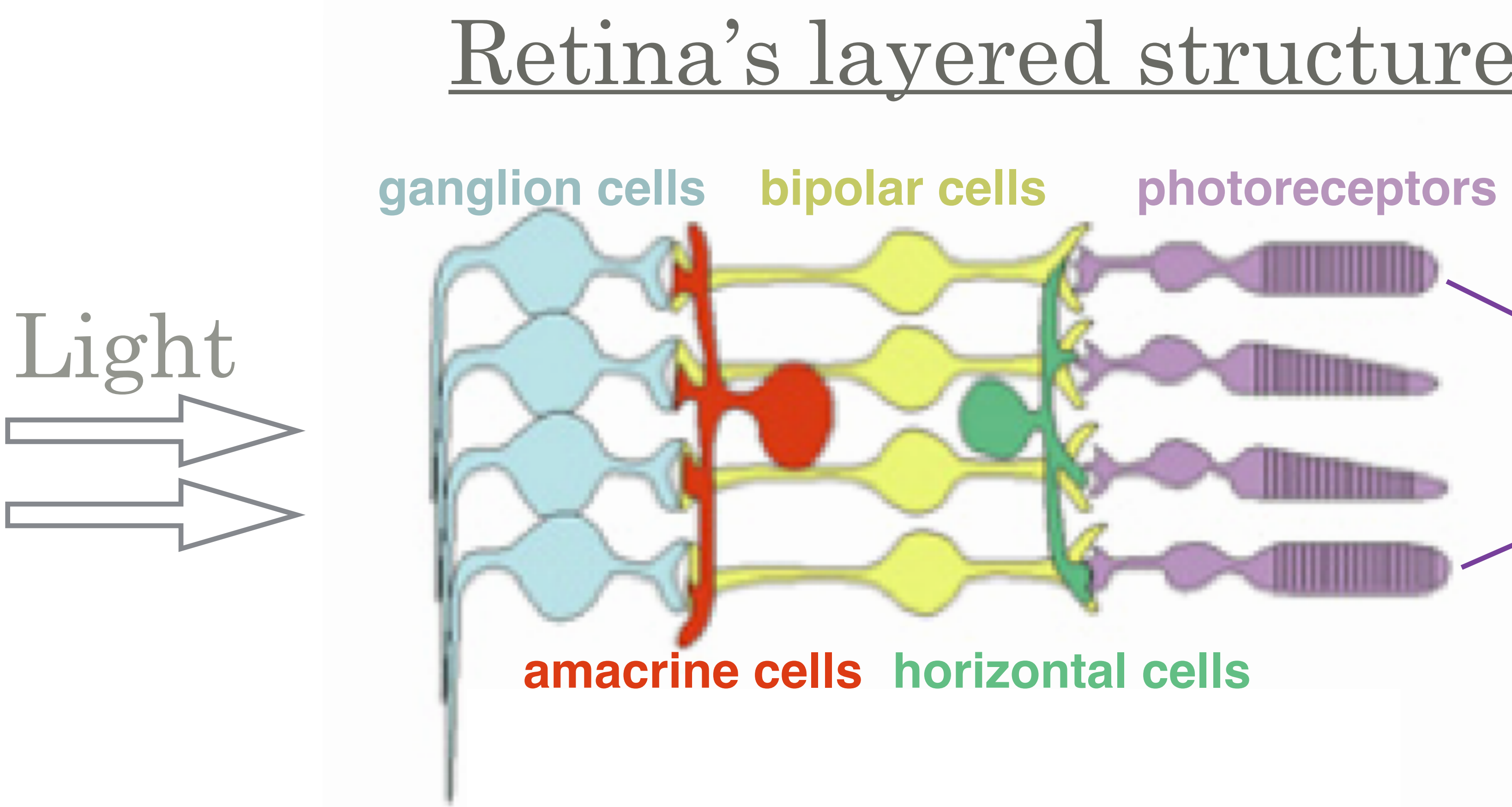
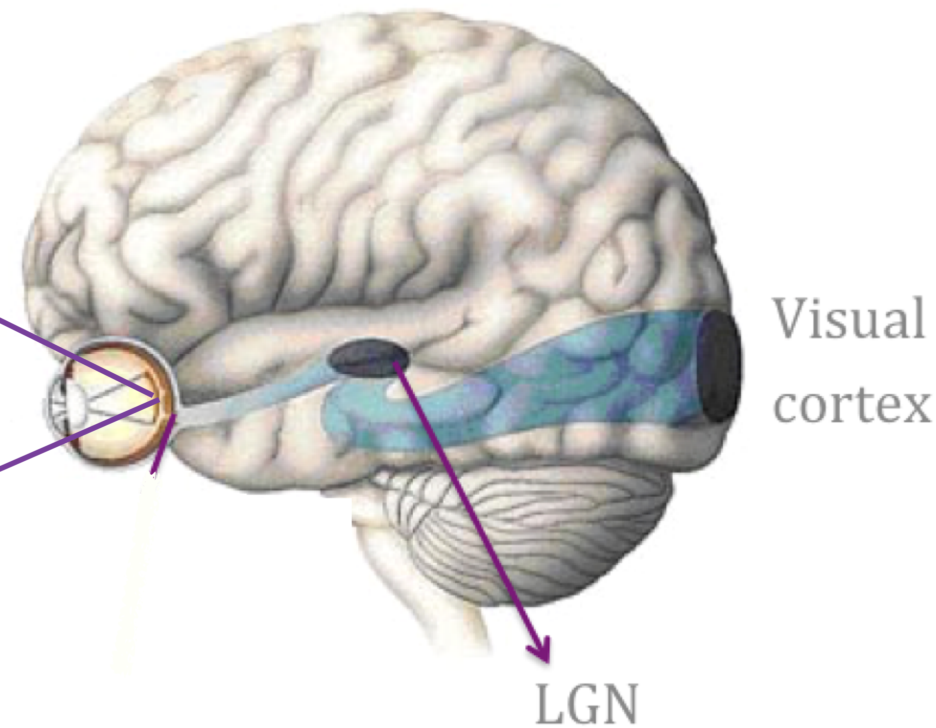
Visual system



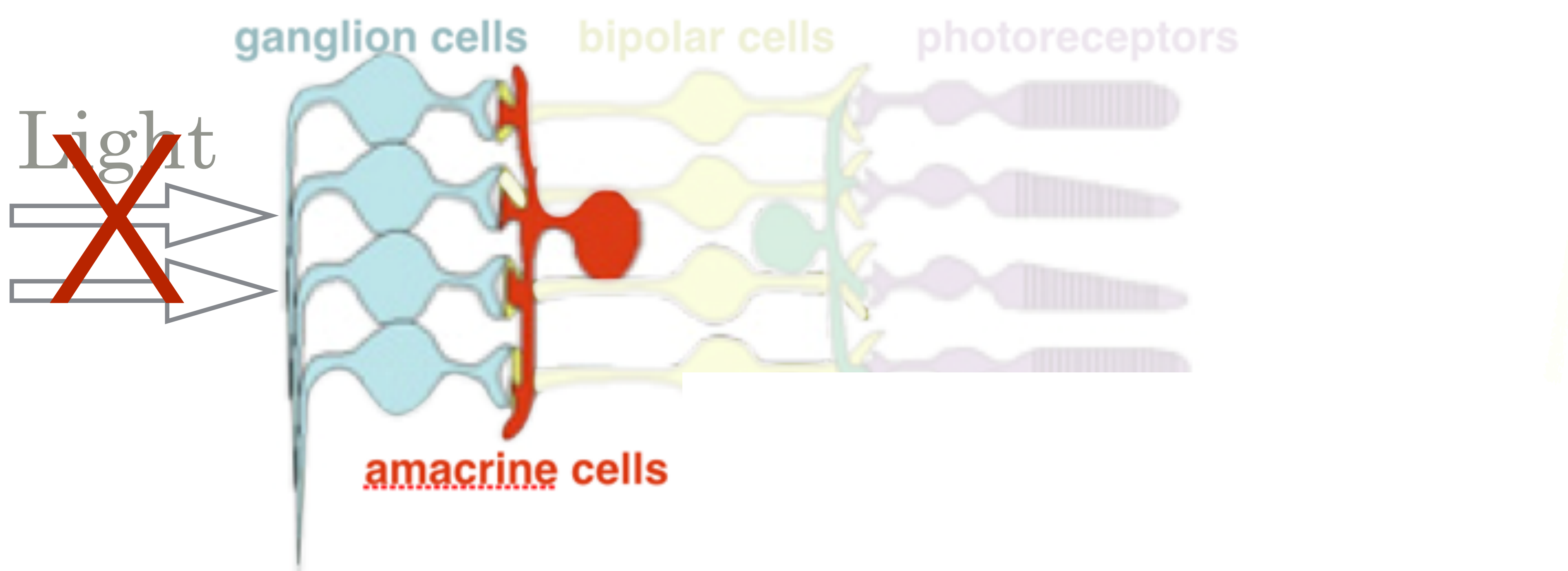
The structure of the adult retina





The structure of the retina <u>during development</u>

<u>Retina's layered structure is shaped during development</u>



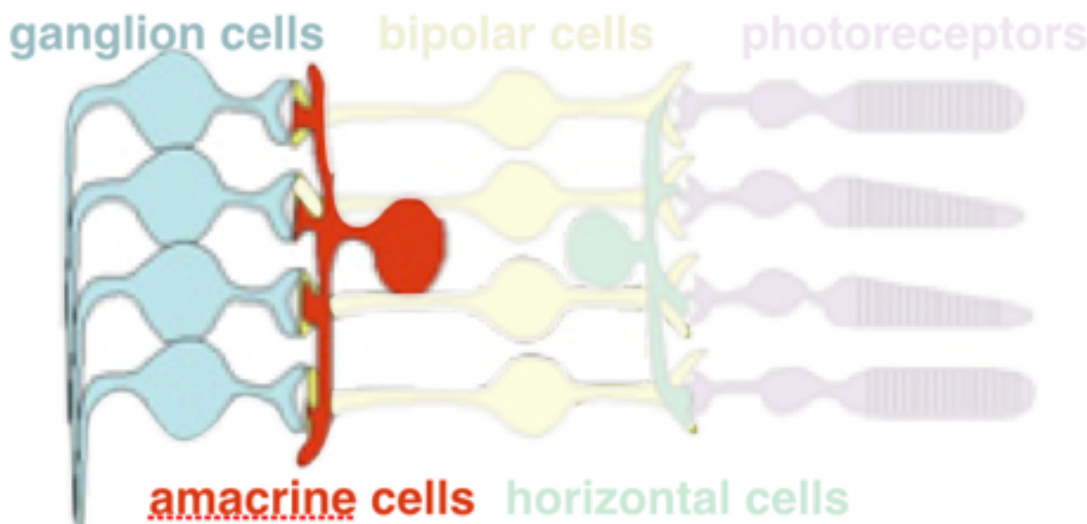
But How? → **Retinal waves!**

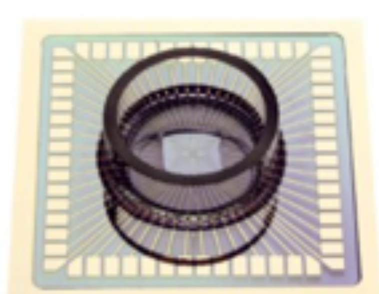
What are Retinal waves?

<u>Spontaneous</u> spatio-temporal waves during development

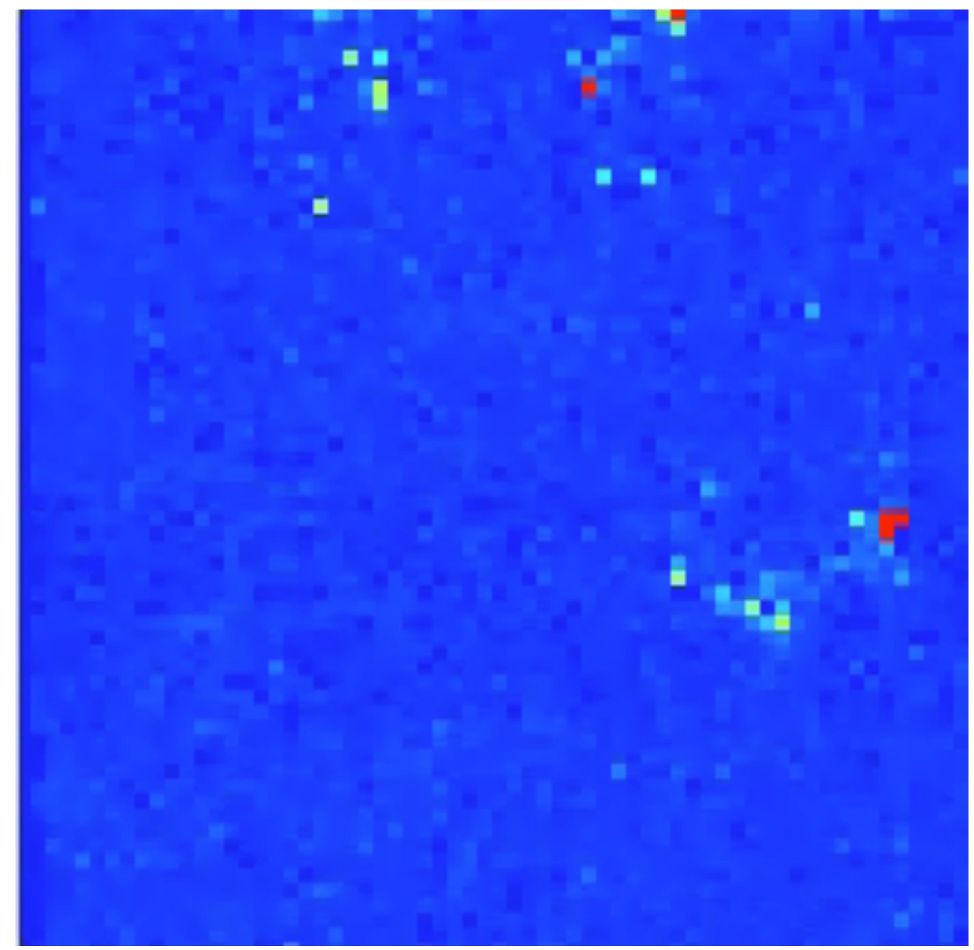
Disappear short after birth when vision is functional

Recordings from the retina





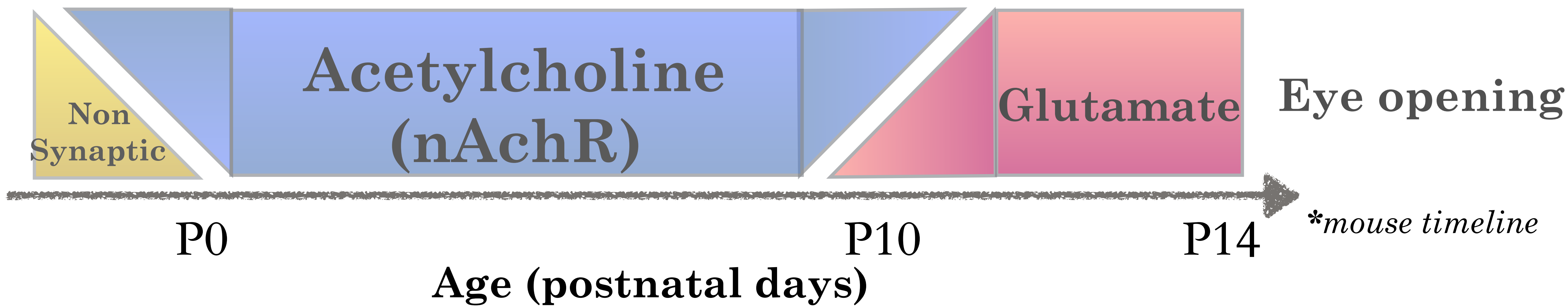
Multi-electrode array (MEA)

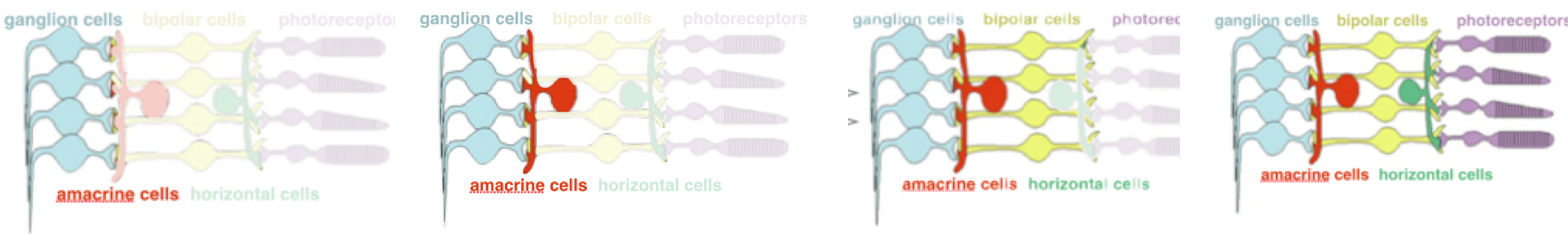


(Maccione et al. 2014)

MEA recording of the voltage from a P11 mouse retina in the presence of 10 μM bicuculline.

The timeline of retinal waves





Stage I

- Formation of early retinal circuitry
- Chemical synapses are not formed yet
- **Electrical synapses mediated**

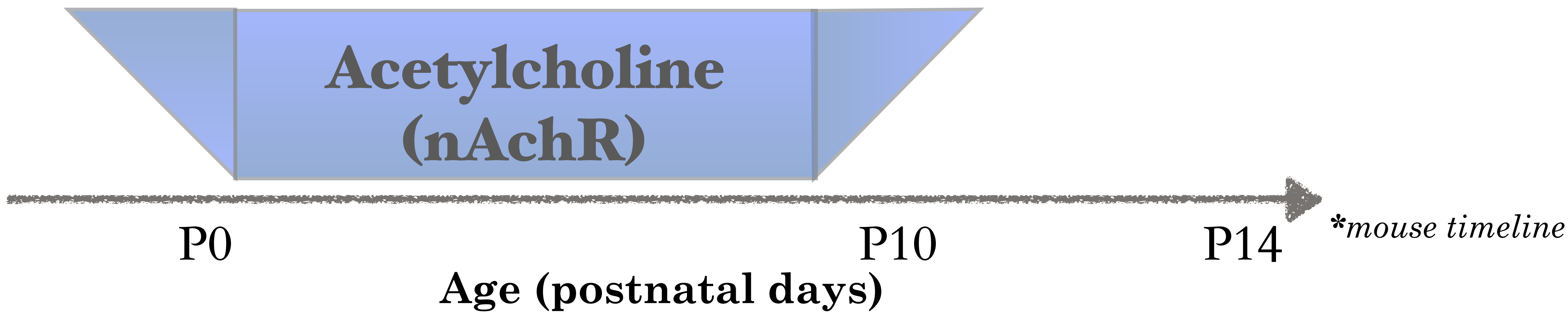
Stage II

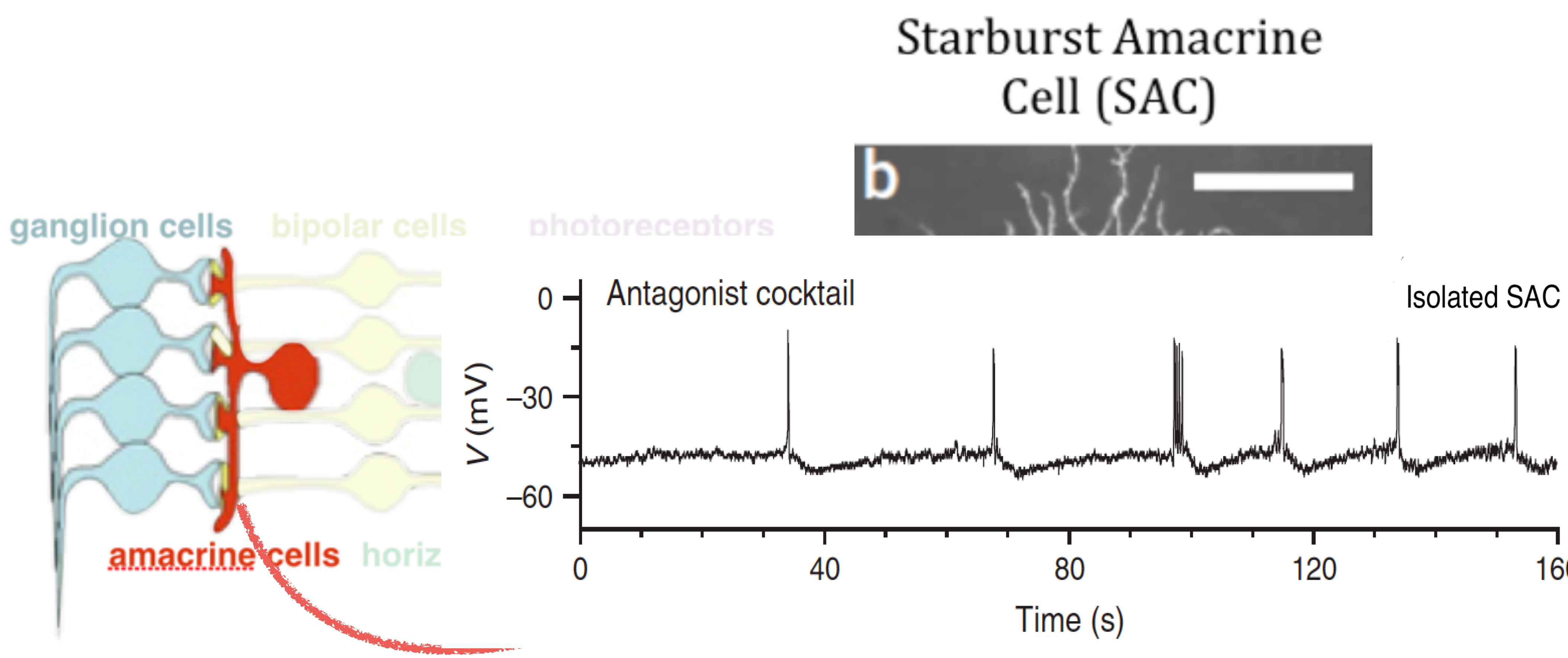
- Retinotopic mapping
- Eye specific segregation
- **Nicotinic Acetylcholine Receptors (nAchR)**

Stage III

- Disappear when vision is functional
- **Glutamate/AMPA Receptors**

Focusing on stage II retinal waves





Zheng et al. 2006

Why modelling retinal waves is an interesting problem?

- Retinal waves **instruct the shaping** of the visual system

- Using biophysical modelling we could
  i) find **generic principles**
  ii) explain **experiments** and propose new ones

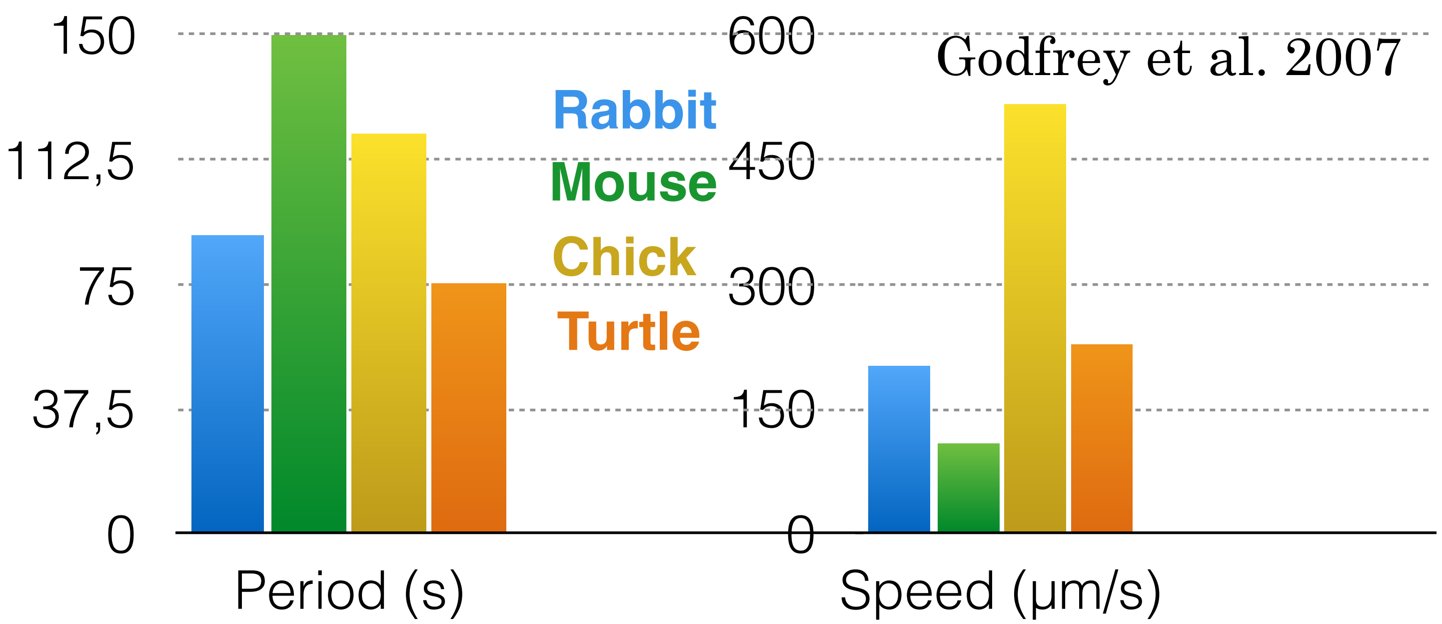
  leading to the better understanding of the underlying mechanisms of waves.

- The mathematical modelling of the dynamics of a complex biological process is a very interesting physical problem with real consequences in biology

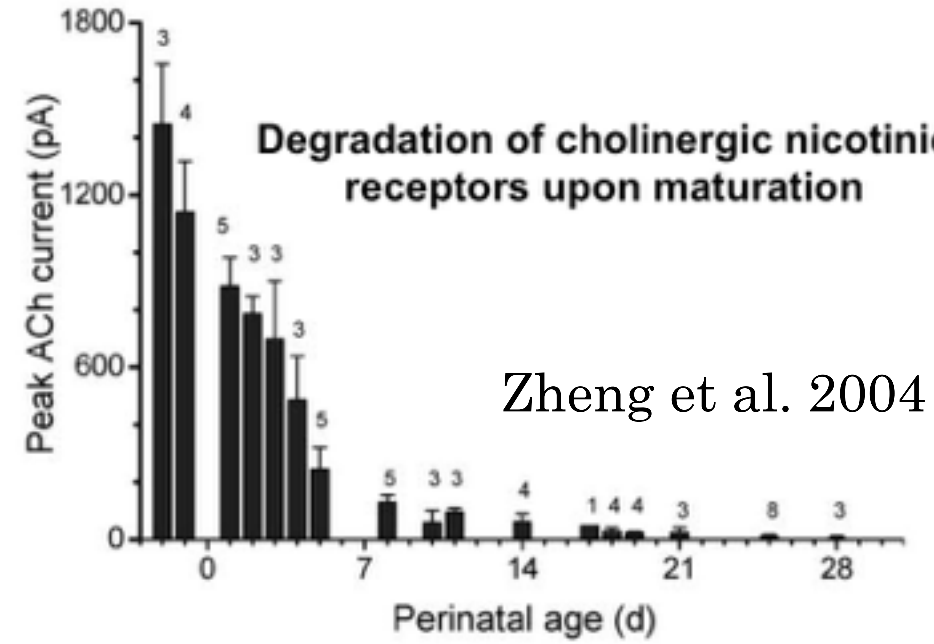
- Understanding the mechanisms that generate them may help to **control them pharmacologically**.

Variability within retinal waves

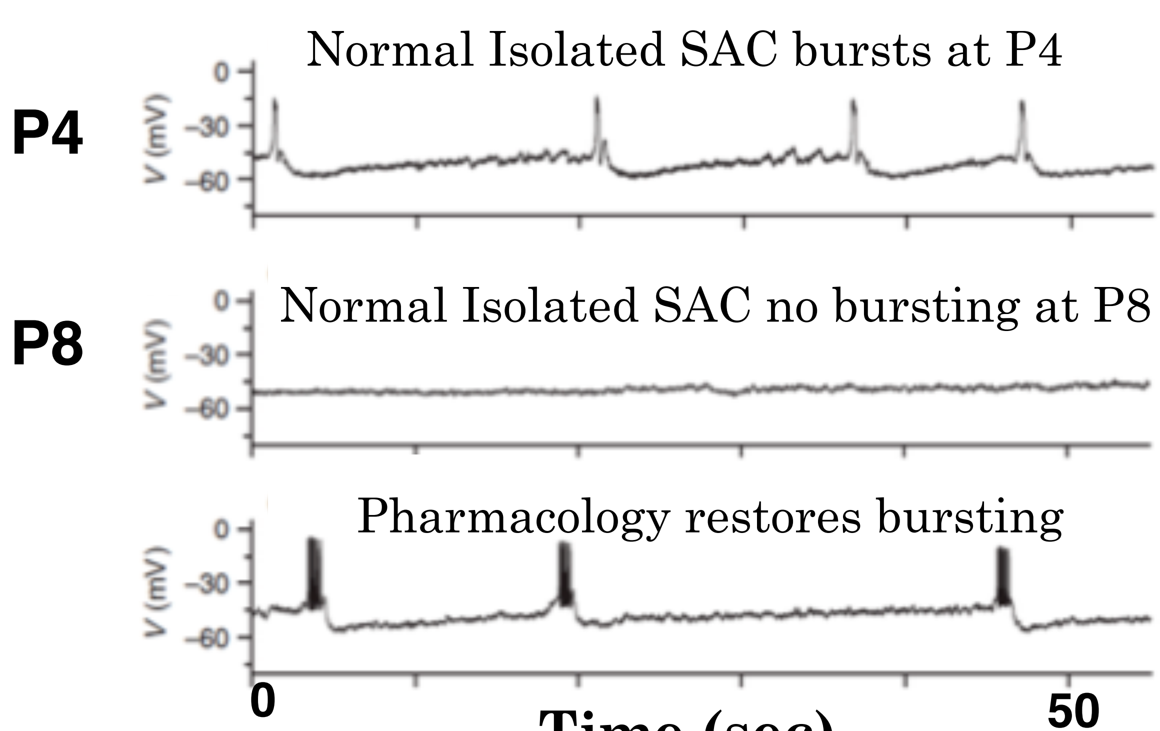
i) Across species



ii) Development

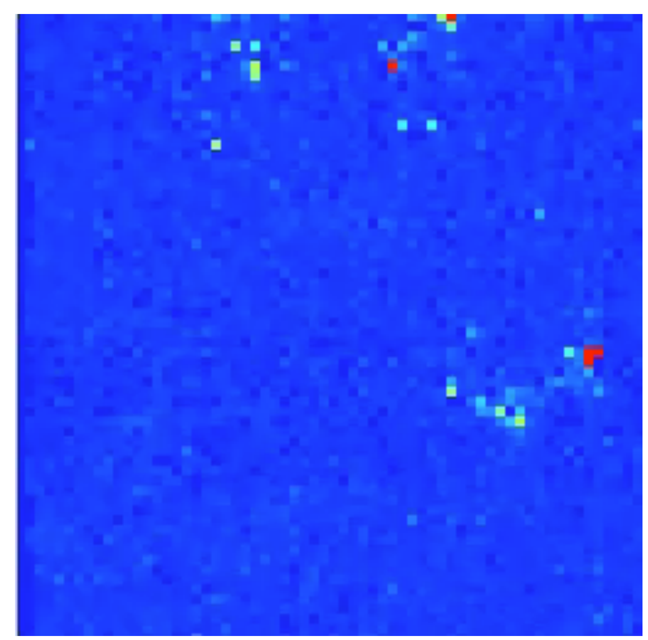


iii) Pharmacology



Zheng et al. 2006

iv) Spatial Variability



Maccione et al. 2014

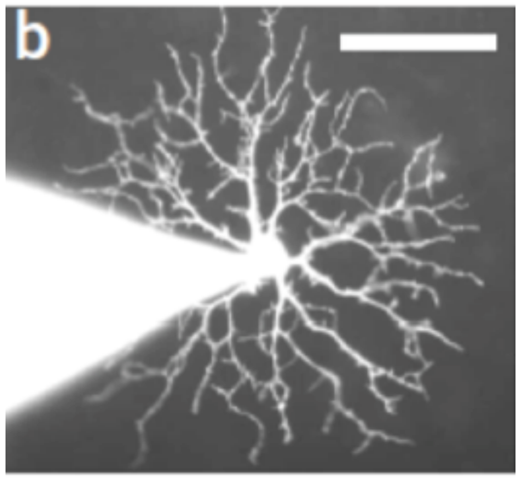
Waves have variable shapes due to a refractory mechanism which controls their borders. It is called sAHP (**s**low **A**fter**H**yper **P**olarization) for stage II.

Modelling stage II retinal waves dynamics

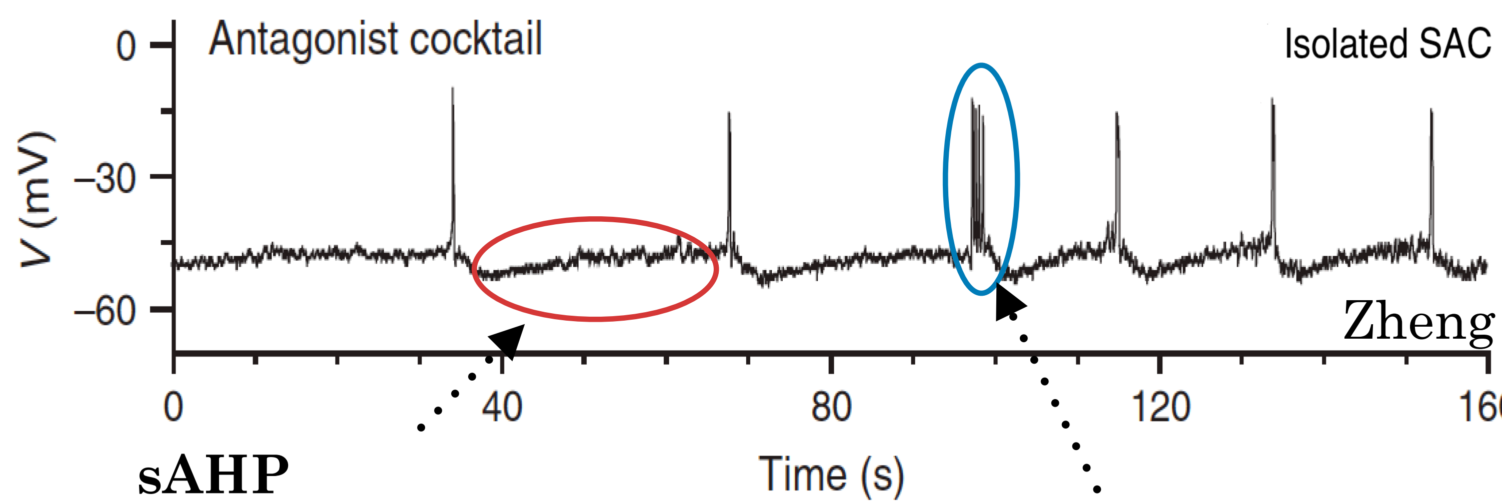
1. D. Matzakos-Karvouniari et al., *A biophysical model explains the bursting activity in the immature retina*, Nat Sci Rep, 2019

The biophysics of stage II retinal waves

Individual SACs burst spontaneously



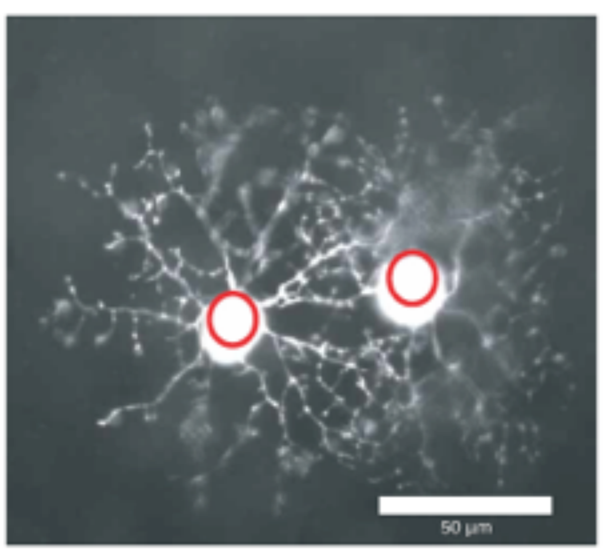
Zheng et al. 2006



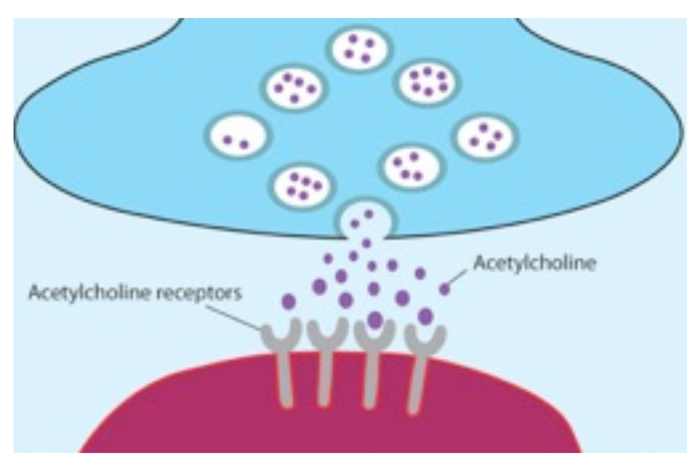
sAHP
(slow AfterHyperpolarization)
Calcium regulated

Spontaneous Fast oscillations

Immature SACs form a transient cholinergic network



Nicotinic Acetylcholine Receptors



Mutual Excitatory synapses

$$g_{Ach} = g_{Ach}^{m} \frac{A^2}{K_d^2 + A^2}$$

A model for stage II retinal waves

Matzakos-Karvouniari et al. 2019, Lansdell et al. 2014, Hennig et al. 2009, Morris-Lecar 1981

6 variables: V, N, C, R, S, A
3 time scales: Fast, Medium, Slow
Nonlinear cholinergic coupling
~30 parameters

Fast

$$
\begin{aligned}
C_m \frac{dV_i}{dt} &= -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) \\
&\quad - g_A (V_i - V_A) \sum_{j \in \mathcal{B}_i} \frac{A_j^2}{\gamma_A + A_j^2} \\
\tau_N \frac{dN_i}{dt} &= \Lambda(V_i)(N_\infty(V_i) - N_i)
\end{aligned}
$$

Medium

$$
\tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C(V_i)(V_i - V_C) \qquad \frac{dA_i}{dt} = -\mu A_i + \beta_A T_A(V_i).
$$

Slow

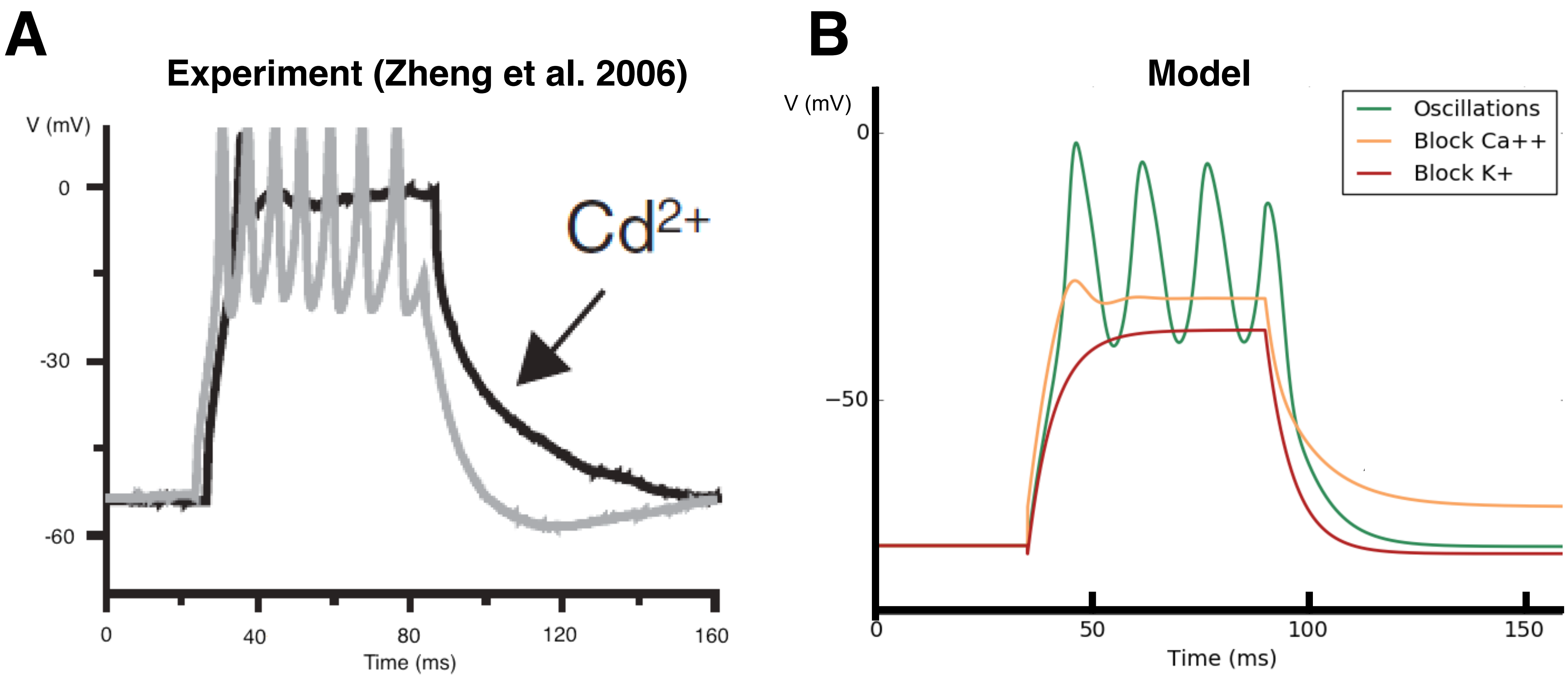
$$
\begin{aligned}
\tau_S \frac{dS_i}{dt} &= \alpha_S (1 - S_i) C_i^4 - S_i \\
\tau_R \frac{dR_i}{dt} &= \alpha_R S_i (1 - R_i) - R_i
\end{aligned}
$$

Fast V, N. $\tau_L = 11$ ms, $\tau_N = 5$ ms.

Medium C, A. $\tau_C = 2$ s, $\tau_A = 1.86$ s.

Slow S, R. $\tau_R = \tau_S = 44$ s.

Validating our equations by reproducing experiments



I. Equations **reproduce** the role of **voltage-gated Ca+2 channels** on fast oscillations
II. We **predict** that a **fast potassium channel** is needed to produce fast oscillations

Analysis through bifurcation theory

How do waves start?

1. D. Matzakos-Karvouniari et al., *A biophysical model explains the bursting activity in the immature retina*, Nat Sci Rep, 2019

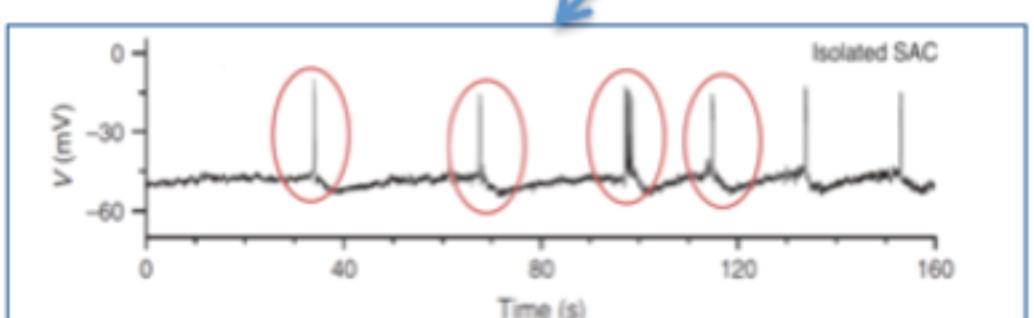
The mechanism of bursting revealed through bifurcations

Fast subsystem

$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

Morris-Lecar & Fast K+ channels



The mechanism of bursting revealed through bifurcations

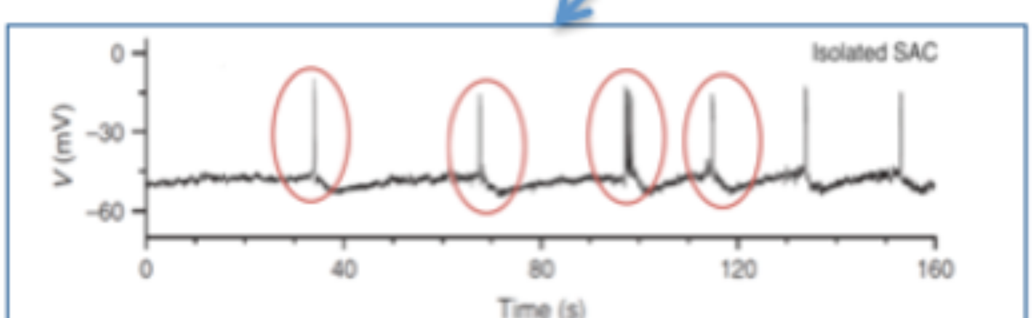
Fast subsystem

$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K) + I_{ext}$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

Morris-Lecar & Fast K+ channels (kV3)

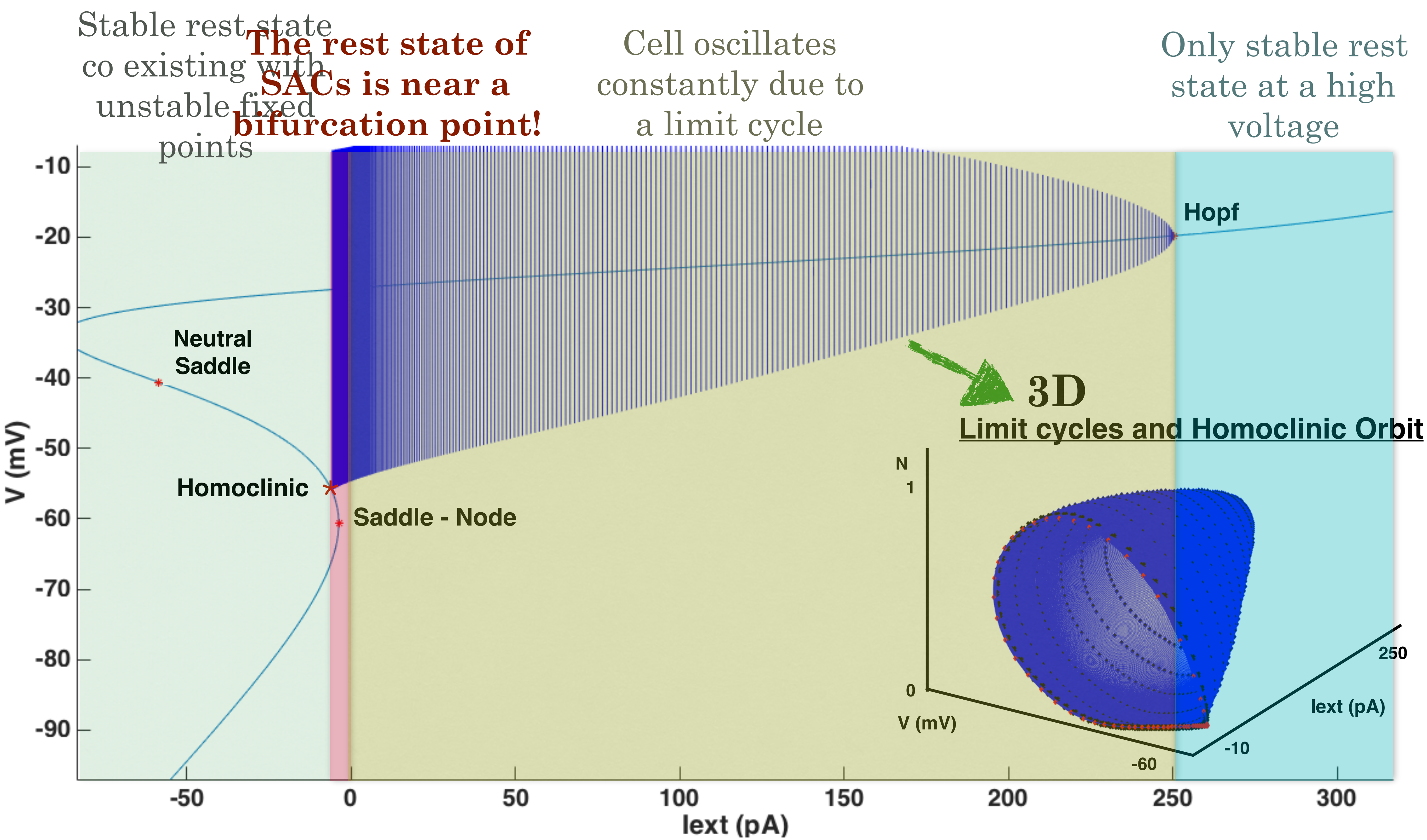
Constant current (bifurcation parameter)



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

I. The SACs repertoire of dynamics upon a current application



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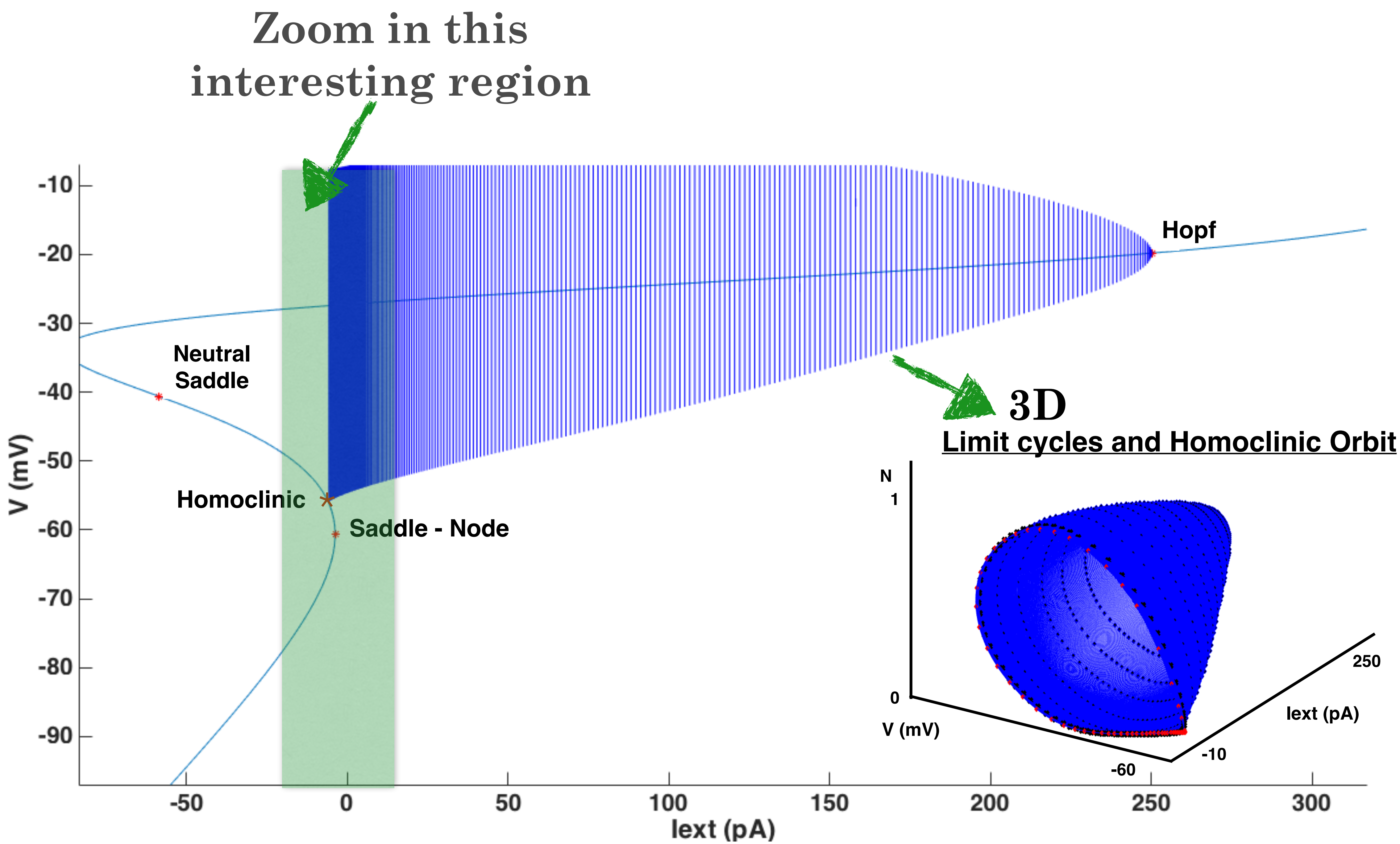

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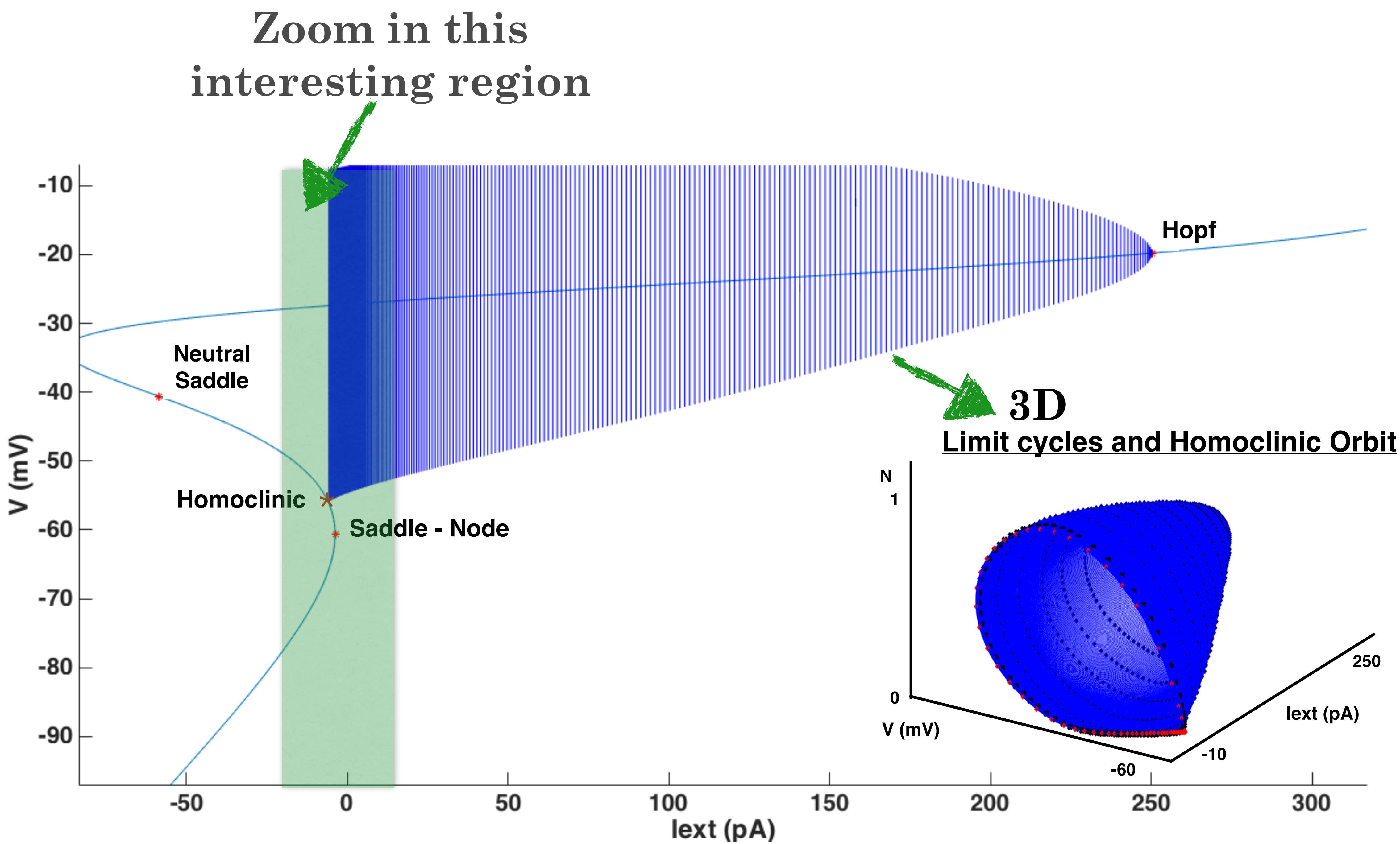
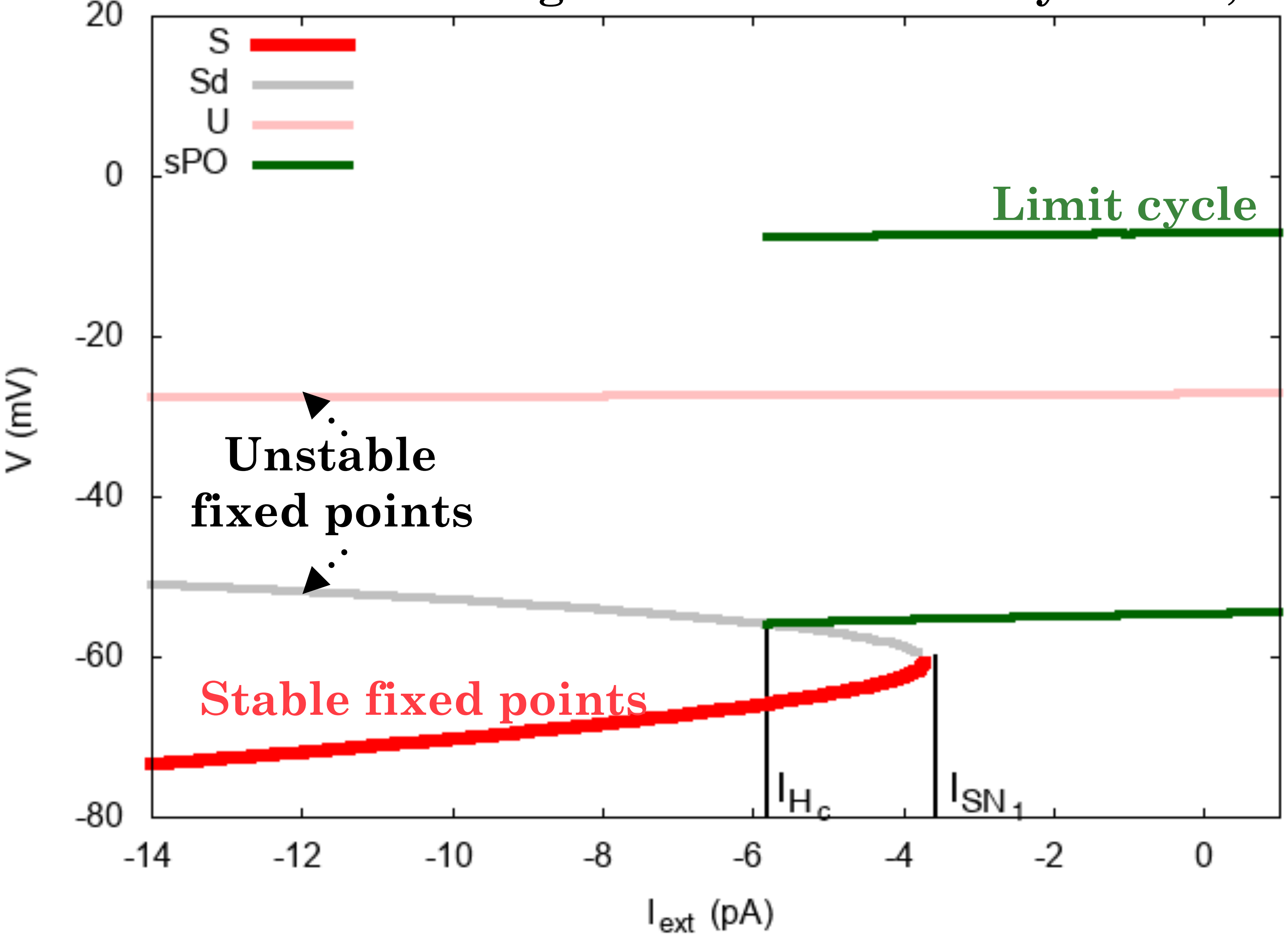


The mechanism of bursting revealed through bifurcations

What do we learn about SACs?

II. The role of sAHP for the bursting mechanism

Bifurcation diagram of the fast subsystem V,N



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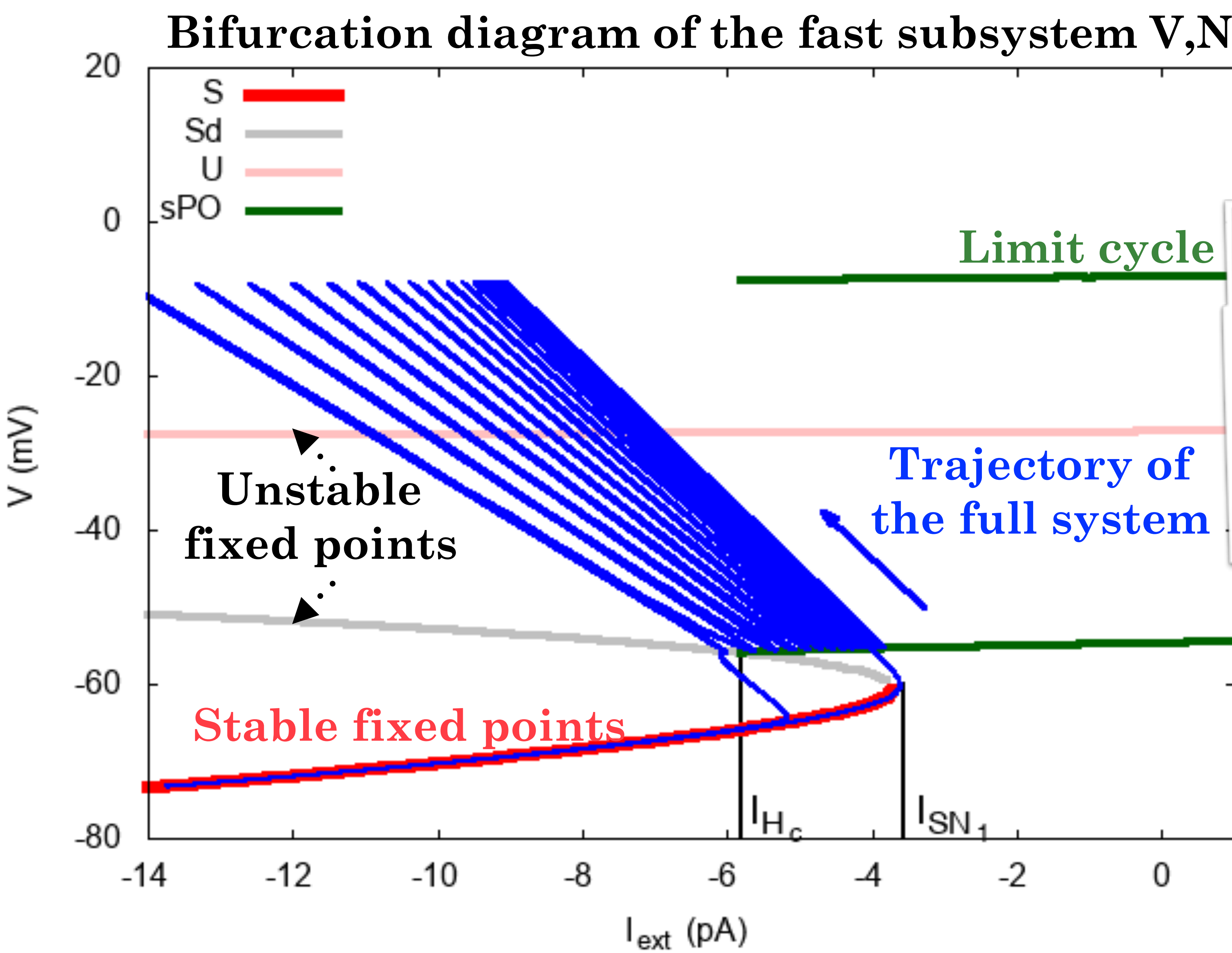
What do we learn about SACs?

II. The role of sAHP for the bursting mechanism

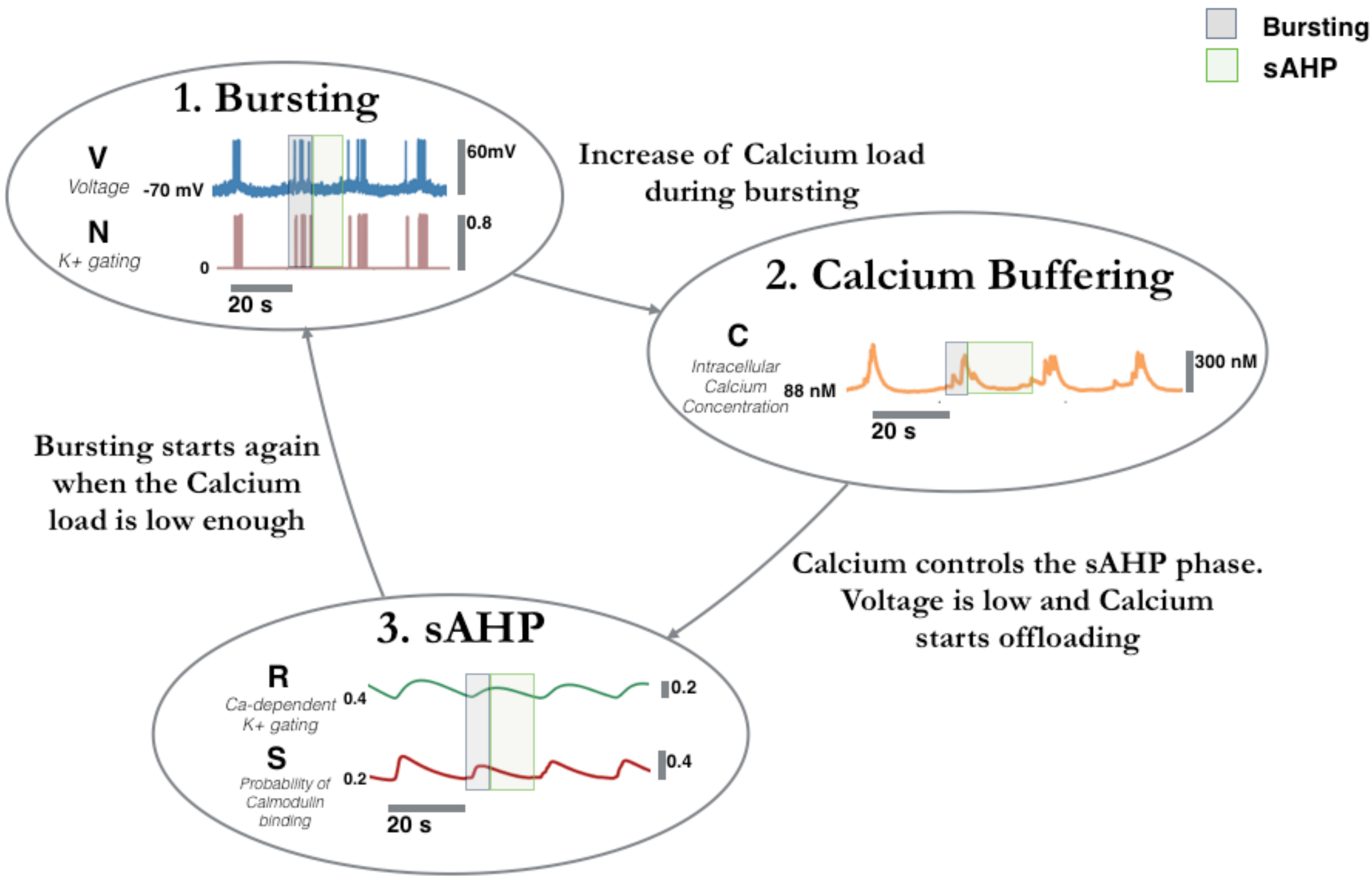


Due to time scale separation, we make the approximation and superimpose the trajectory of the full system on the bifurcation diagram

$$I_{sAHP} = g^{m}_{sAHP} R^4 \left(V - V_K\right)$$

The mechanism of bursting revealed through bifurcations

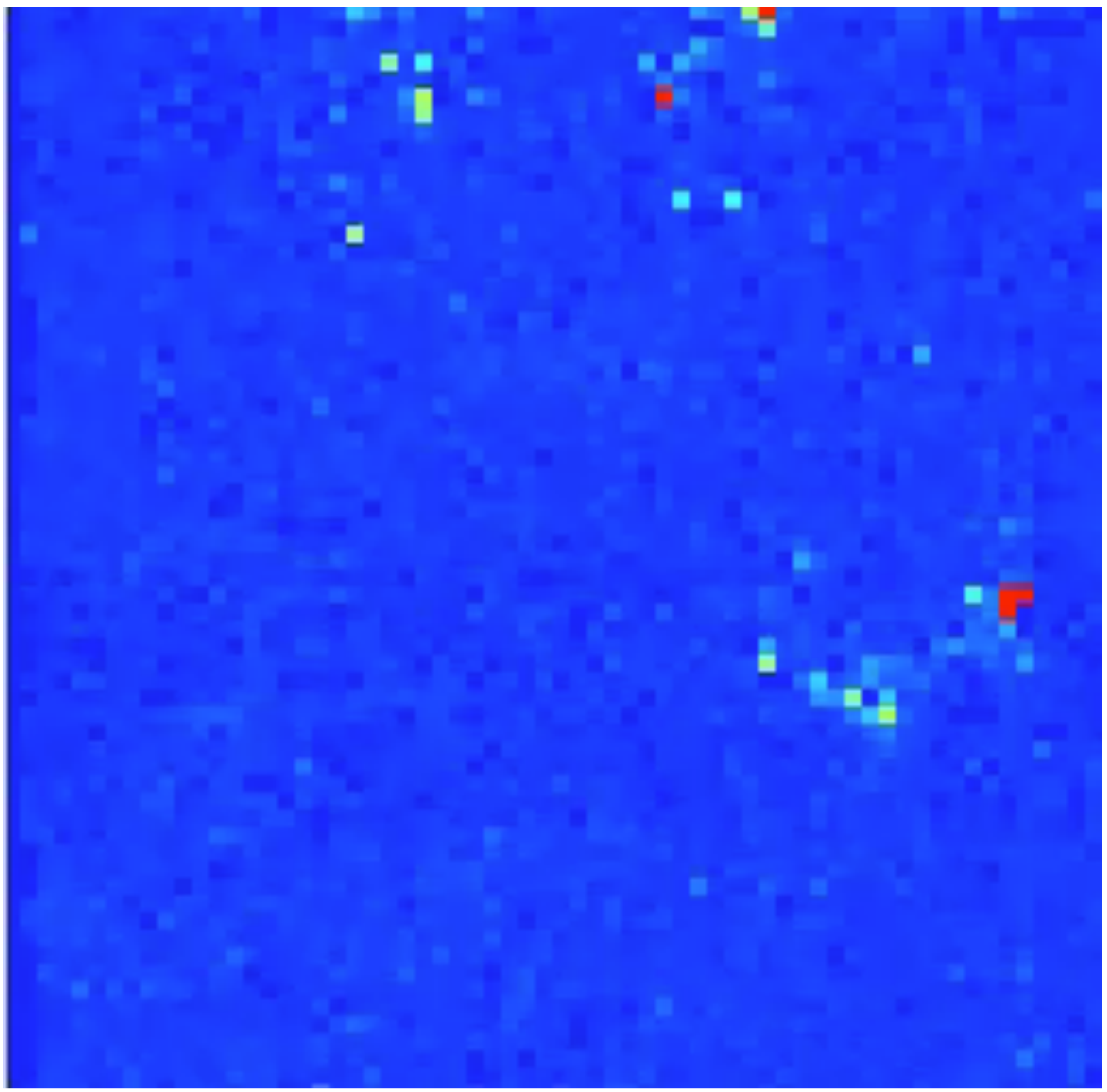
The biophysical interpretation



How do waves propagate and stop?

2. D. Karvouniari et al., *Spontaneous emergence of spatio-temporal structure in the early retina*, (under preparation for Phys. Review E)

How do waves propagate?



- **Full interacting waves are a complex paradigm**
- **Waves propagate in a landscape changing constantly**
- **It is hard to extract a mechanism of propagation**

A network model of stage II retinal waves

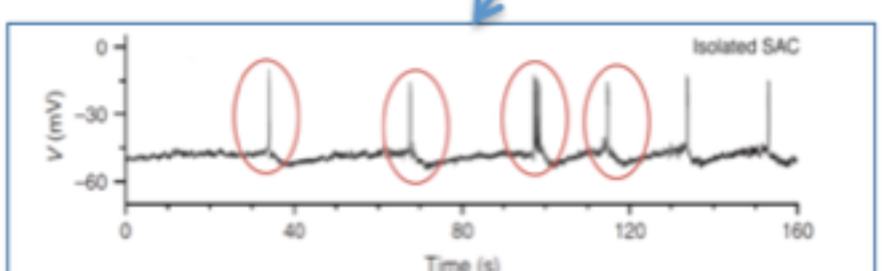
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M(V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i(V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach}(A_j)(V_i - V_{Ach})$$

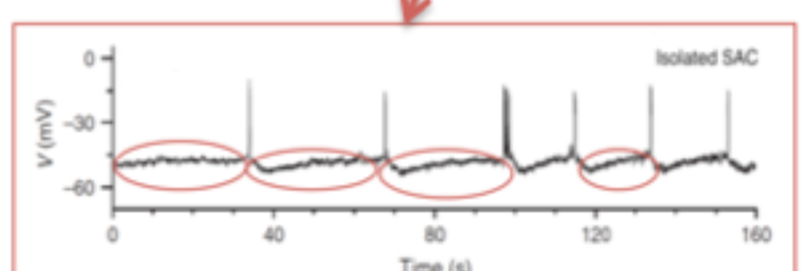
$$\tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i)$$

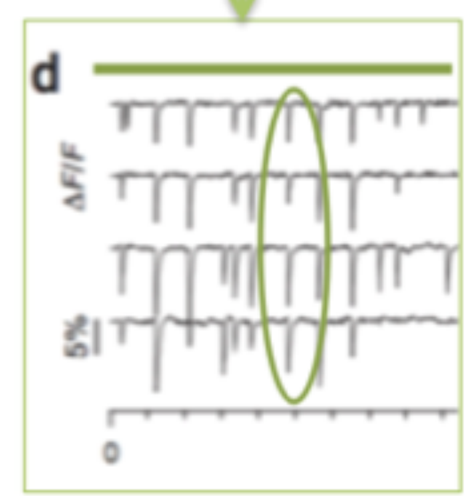
Morris-Lecar & Fast K+ channels

sAHP current
Refractory mechanism

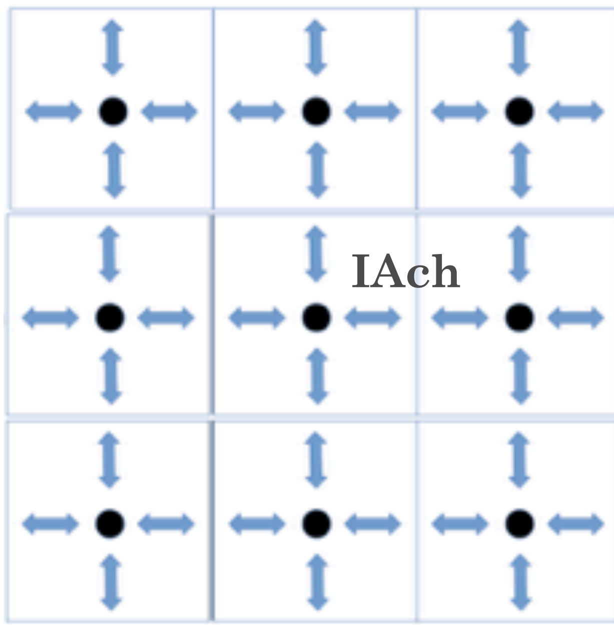
Ach current
Network effect



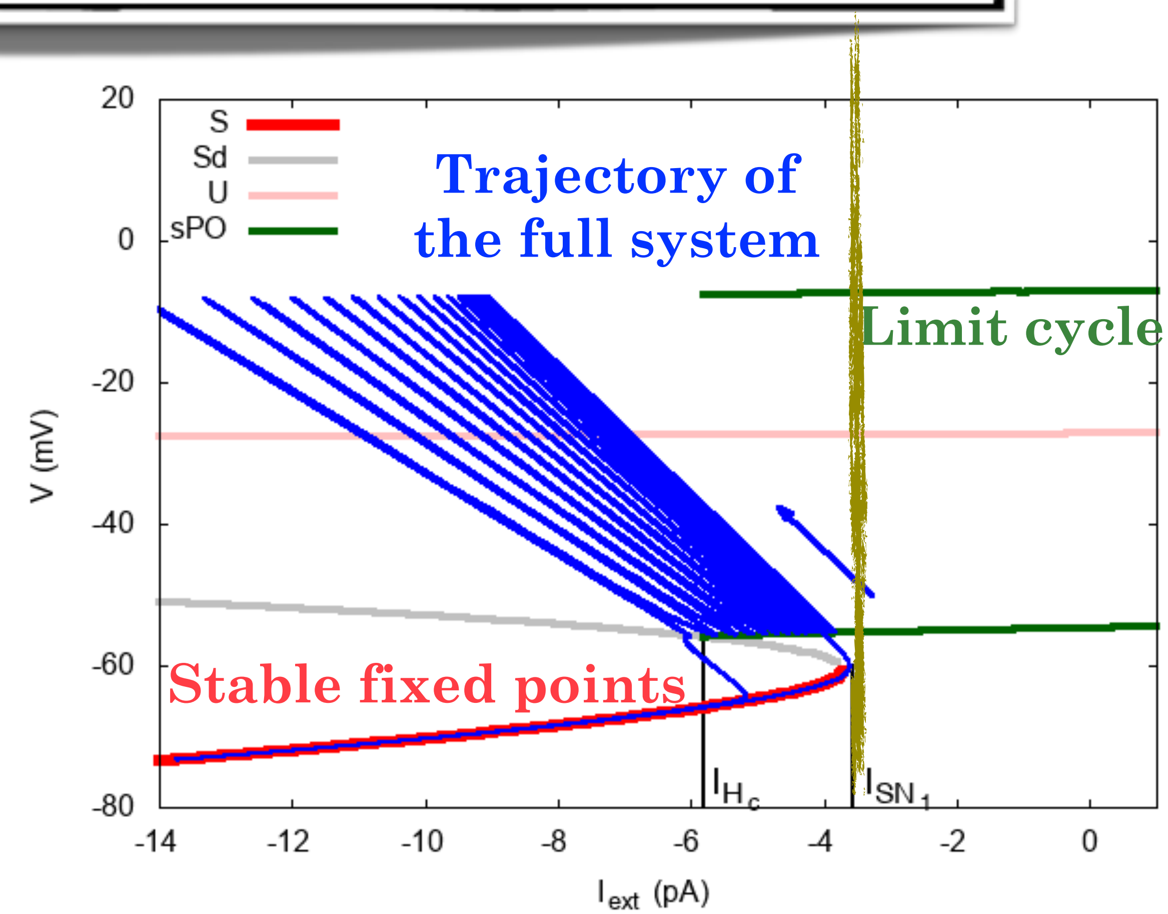




Condition for wave propagation: IAch+IsAHP=ISN



SACs become points on a lattice



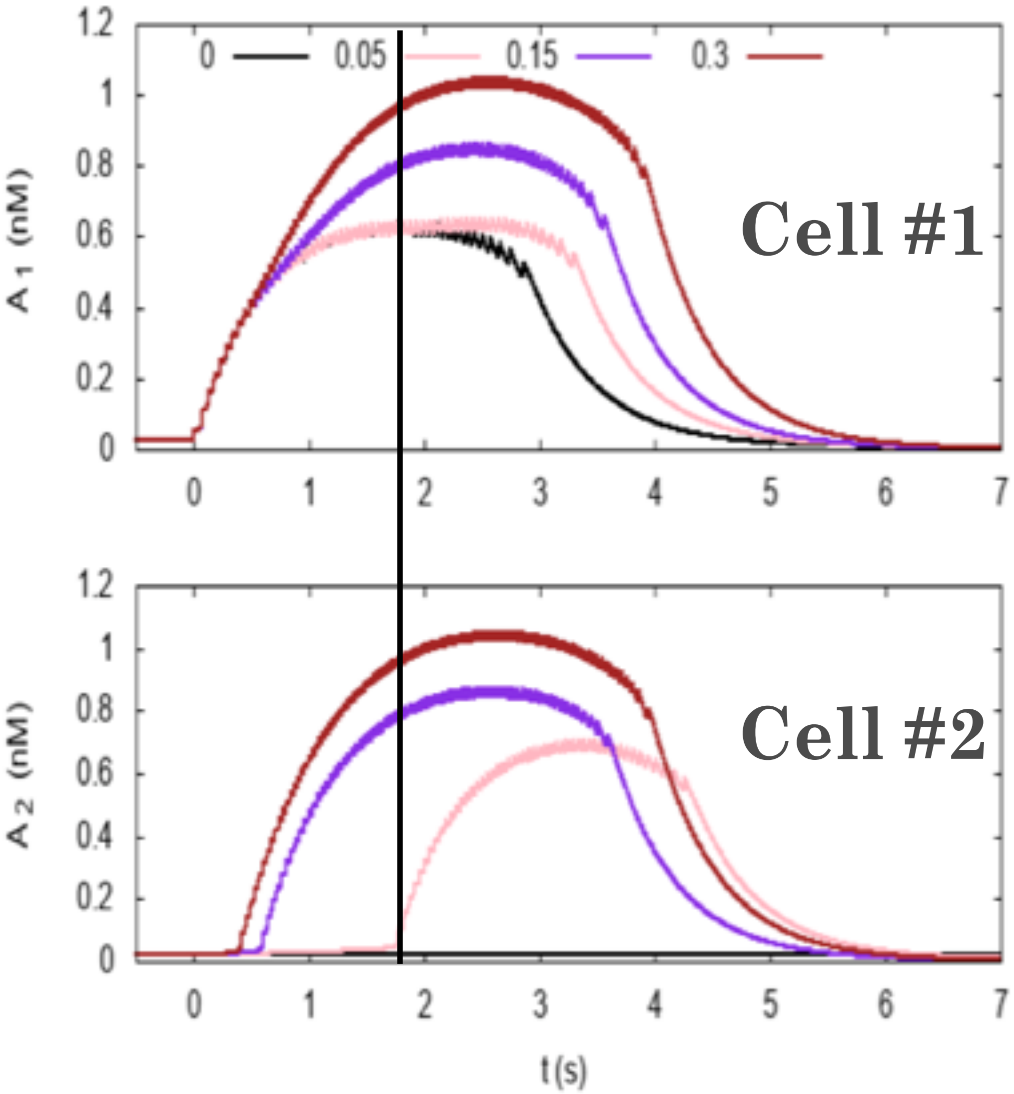
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M\left(V_i - V_L\right) - g_{Ca}\left(V_i\right)\left(V_i - V_{Ca}\right) - g_K N_i\left(V_i - V_K\right) + I_{Ach} + I_{sAHP}$$

$$\downarrow$$

$$\tau_N \frac{dN_i}{dt} = \Lambda(V_i)\left(N_\infty(V_i) - N_i\right)$$

The coupled dynamics of 2 SACs

Ach profile



Condition for bursting to start:
$I_{Ach} + I_{sAHP} = I_{SN}$

Response Time

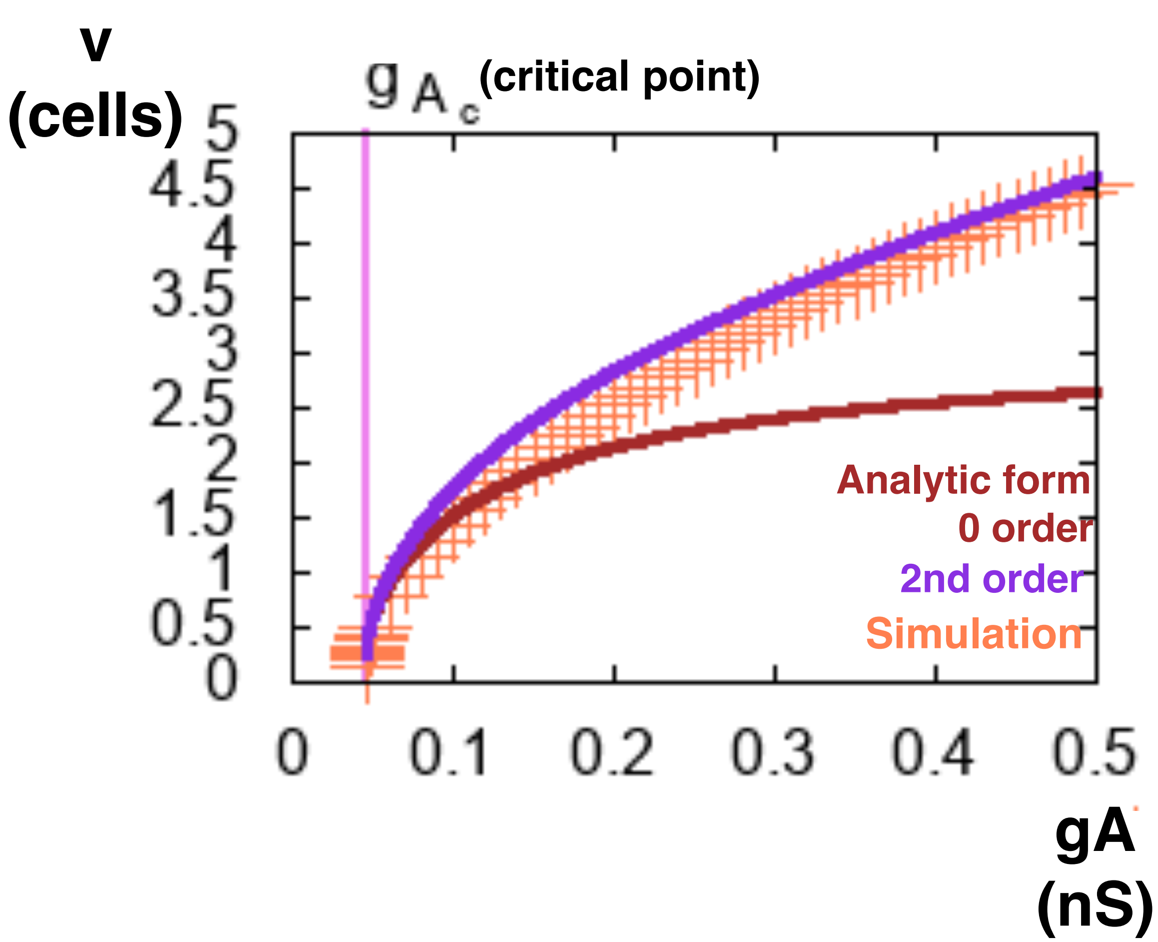
$$t_i = -\frac{1}{\mu}\log\left(1 + \frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega}\left(\frac{I_{SN} + g_{sAHP}R^4(V_- - V_K)}{g_A(V_- - V_A)}\right)\right)$$

Waves speed

$$v_0 = \frac{1}{t_C - \frac{1}{\mu}\log\left(1 + \frac{1}{g_A}\frac{2\mu\sqrt{\gamma_A}}{d\beta\Omega}\left(\frac{I_{SN} + g_{sAHP}R^4(V_- - V_K)}{(V_- - V_A)}\right)\right)}$$

Analytic form of waves propagation coupling threshold

- **Waves speed (1D)**



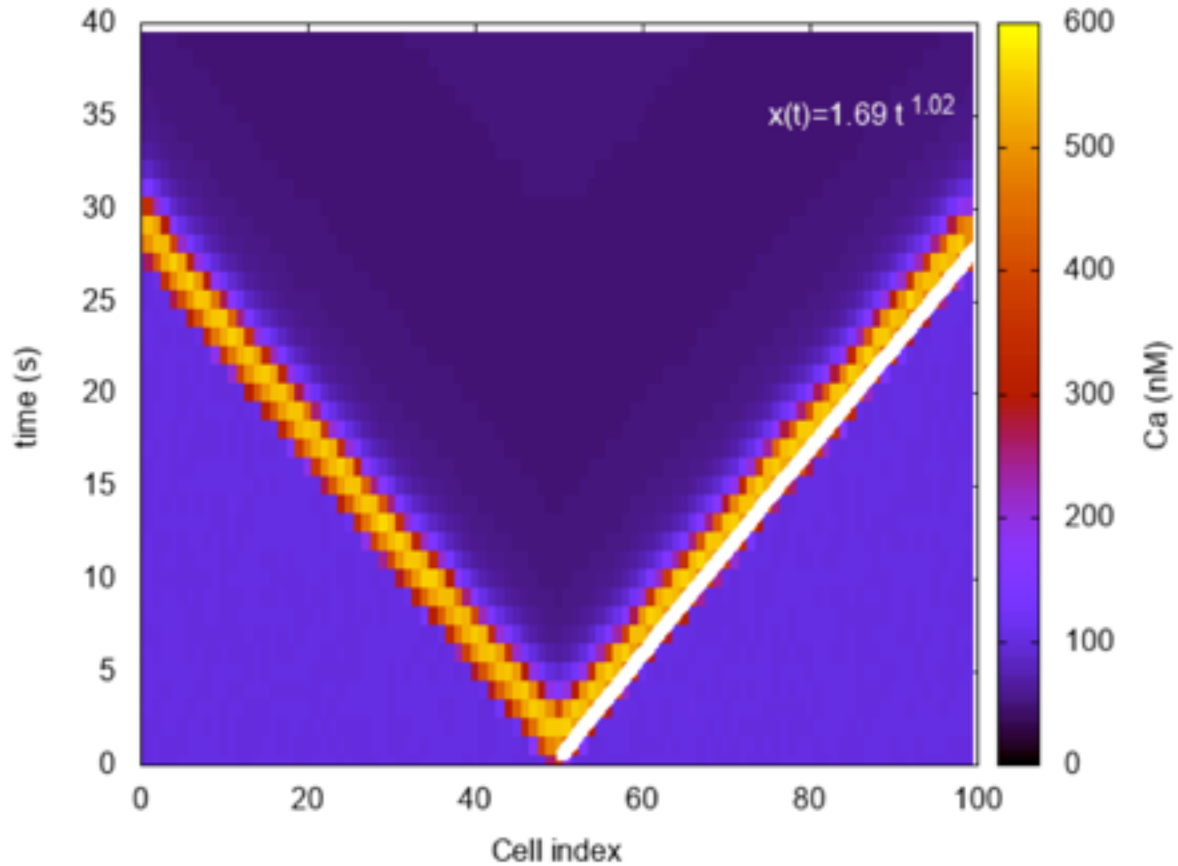
Based on our model, where wave propagation is only possible when the **total current received by a neighbouring cell exceeds the** (saddle-node) **bifurcation threshold**, we extract the analytic form for the waves propagation coupling threshold (1D case).

$$g_{A_c} = -\frac{2\,\mu\sqrt{\gamma_A}}{n_i \beta \Omega}\,\frac{I_{SN} + g_S R^4 (V_- - V_K)}{V_- - V_A}$$

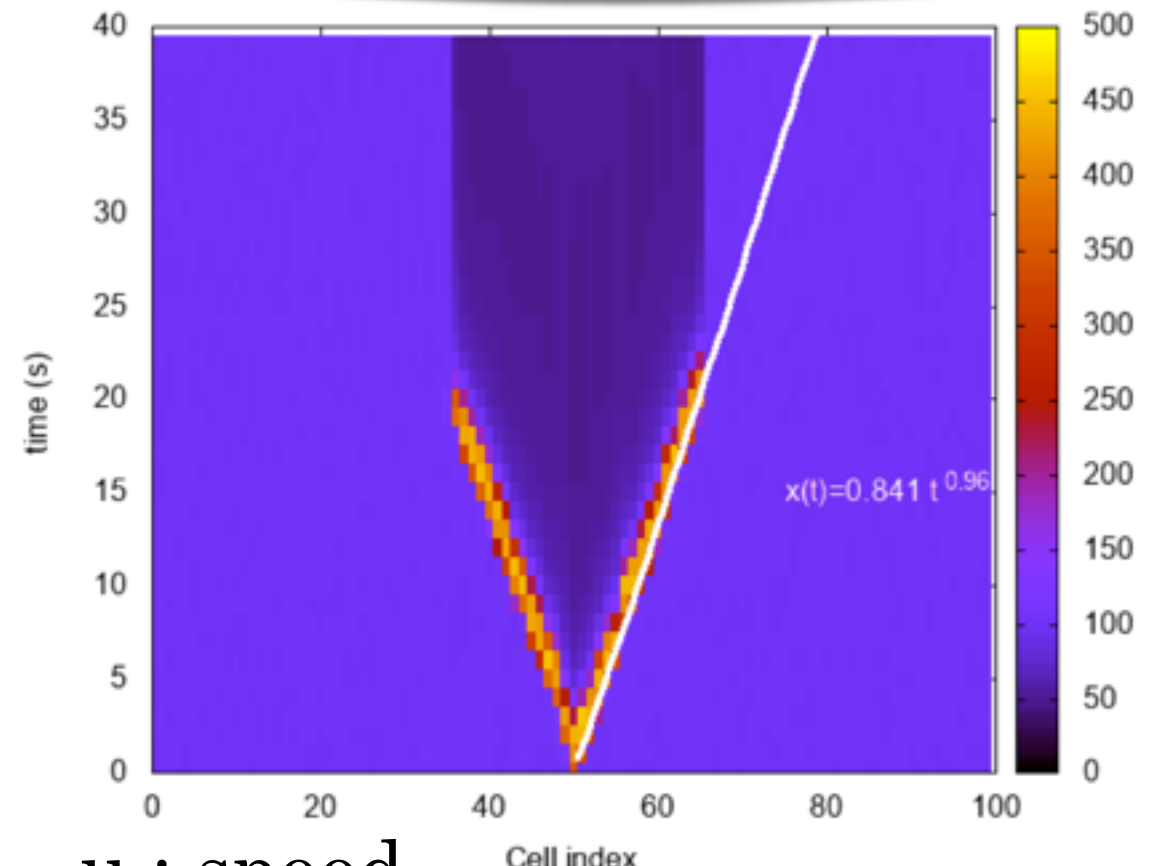
- For the zero order approximation we assumed that V_, R and Ω do not depend on gA. **Fit holds for smaller gA**

Propagation in 1D without friction

$$\boxed{g_A > g_{A_c}}$$



$$\boxed{g_{A_c} = -\frac{2\,\mu\sqrt{\gamma_A}}{n_i\beta\Omega}\,\frac{I_{SN} + g_S R^4(V_- - V_K)}{V_- - V_A}}$$



Fitting trajectory:

$$\langle\rho\rangle = \rho_0 + vt^z$$

u : speed

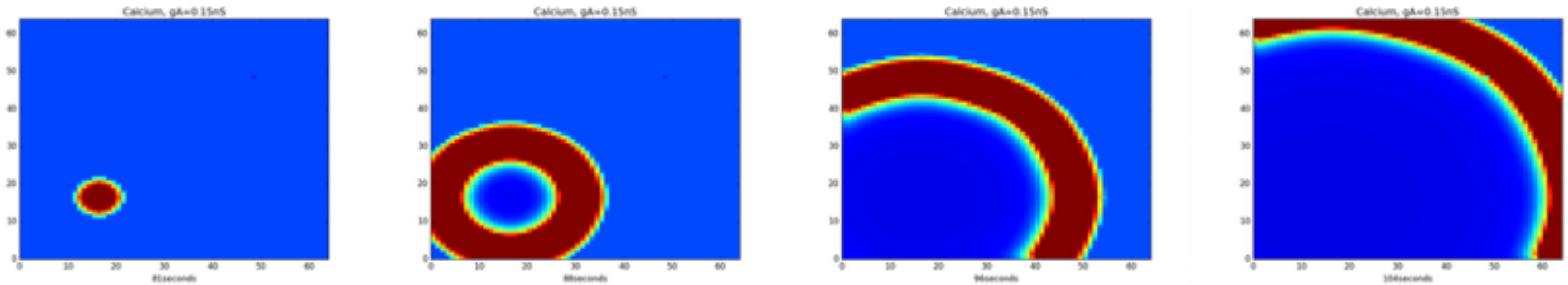
z : propagation exponent

(e.g. z=1 ballistic)

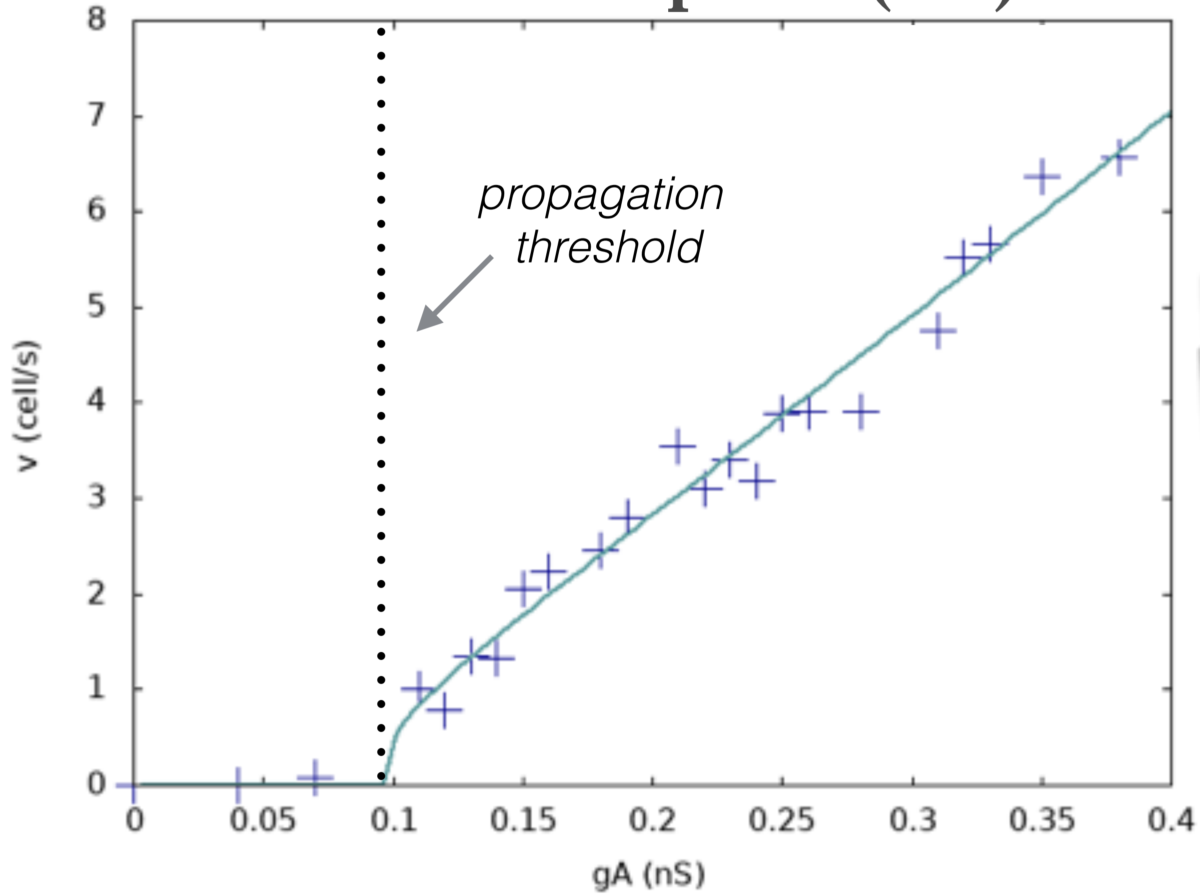
- Around the propagation threshold, waves could stop even without friction, due to noise and the fact that the Ach current is not sufficient to fulfil the propagation condition

Propagation in 2D without friction

Approximation, free propagation no friction, all cells are at rest

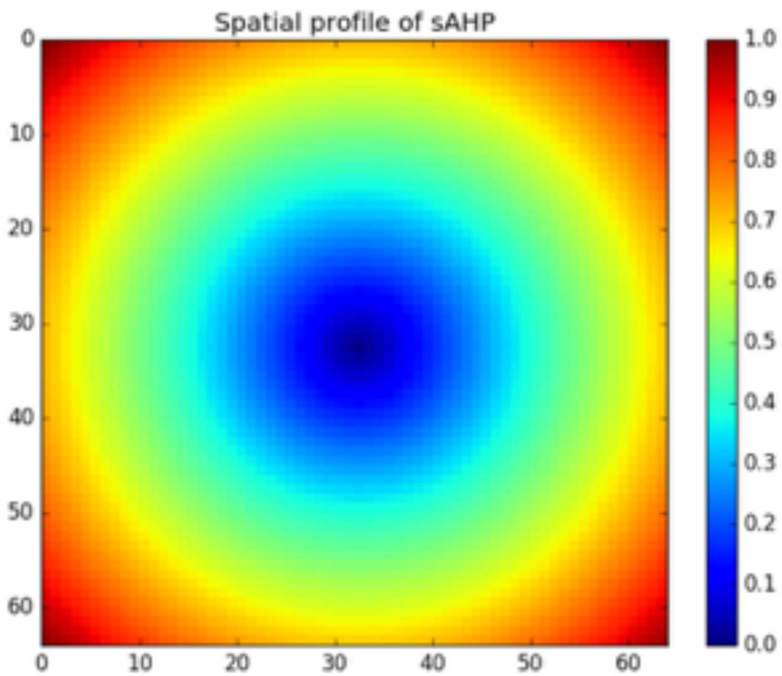


Waves speed (2D)

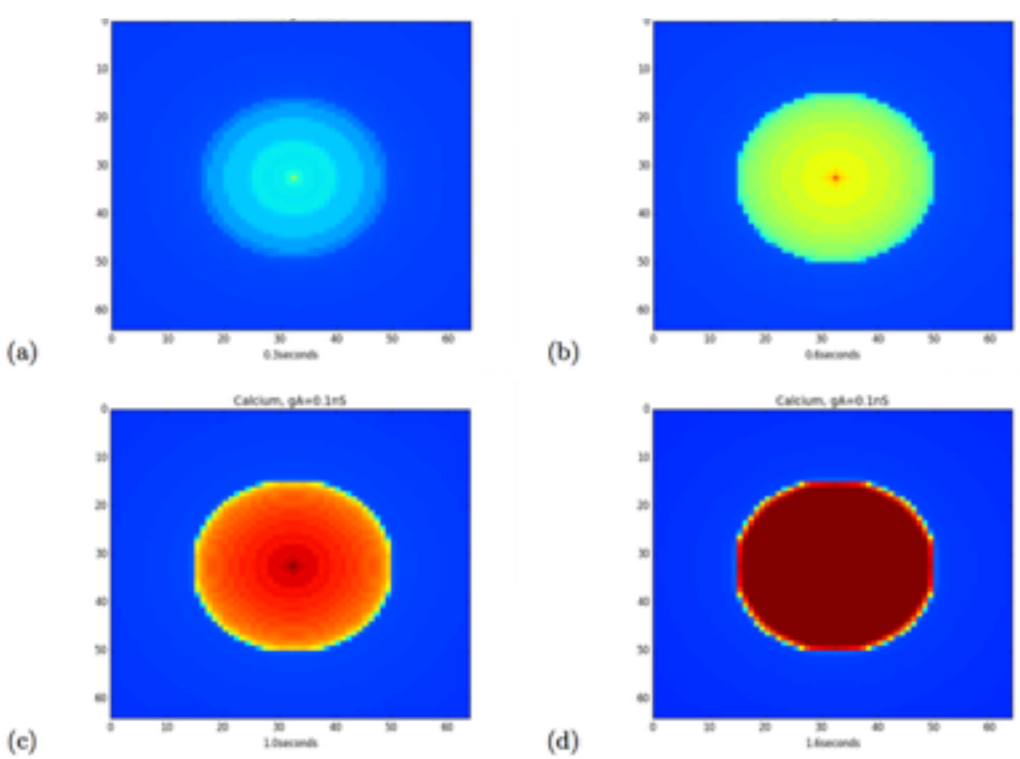


- **The speed increases with the coupling strength**

How do waves stop? The sAHP saga

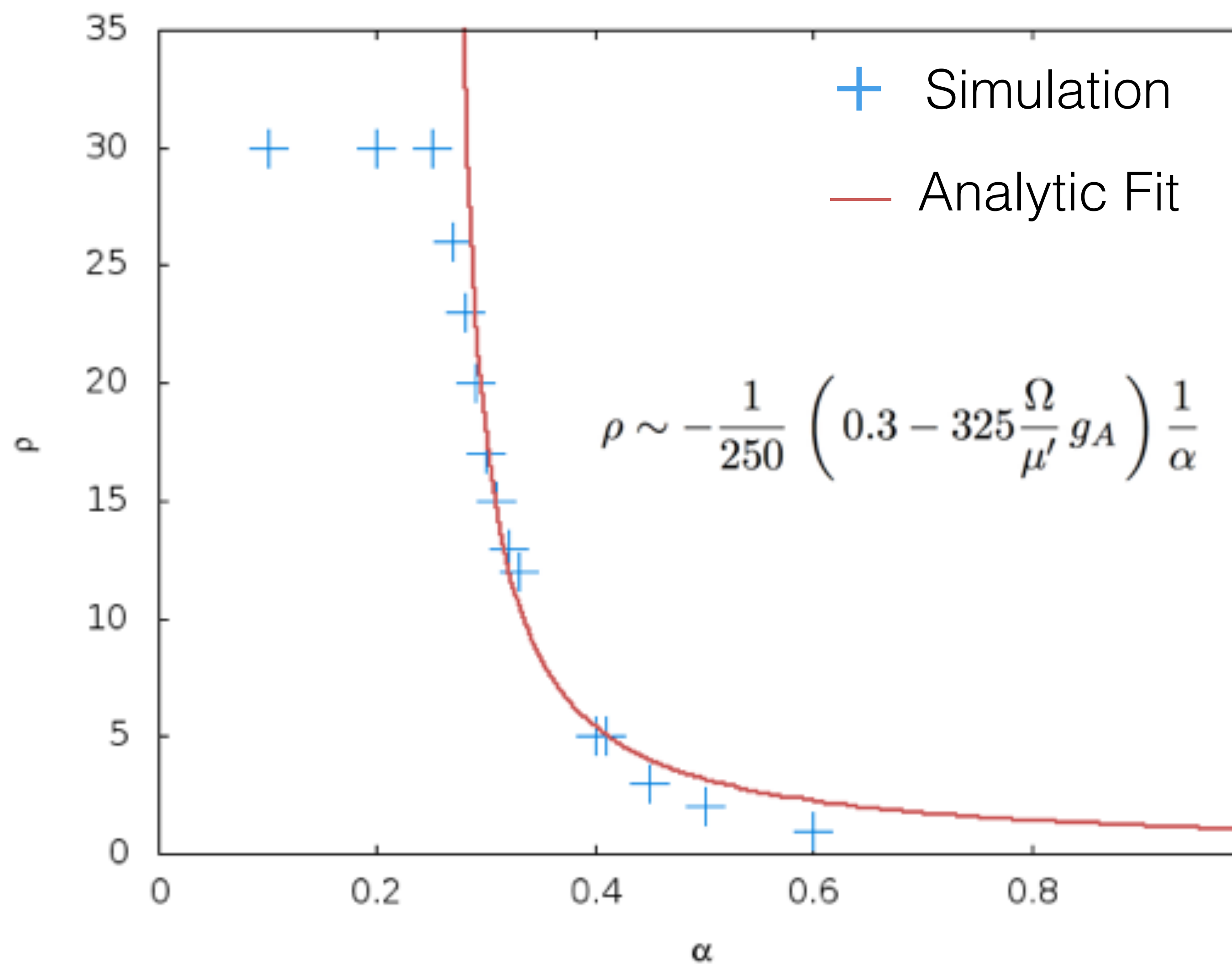


$$R_s = \alpha d^{1/4}$$



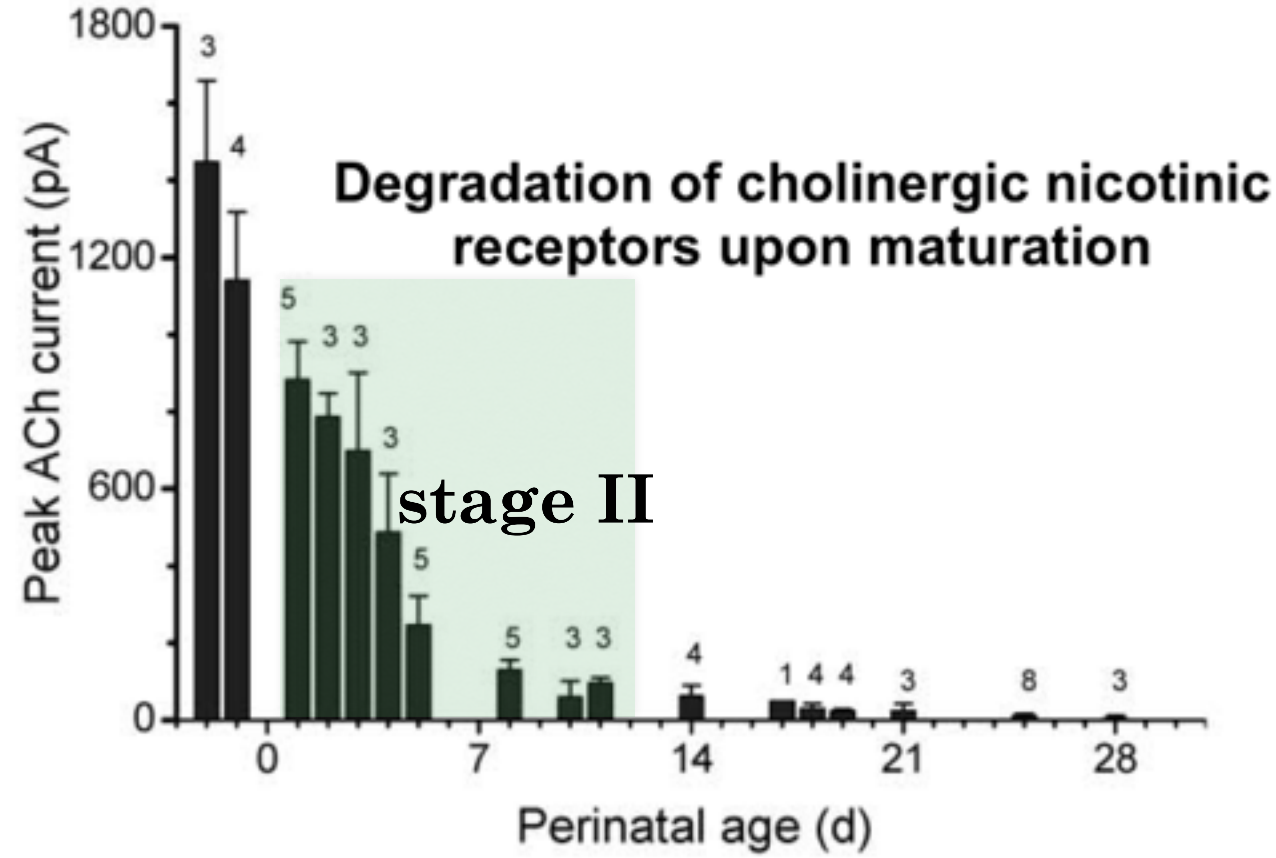
Example of a wave propagation in a radial landscape of R

Max Waves size as a function of the strength of sAHP

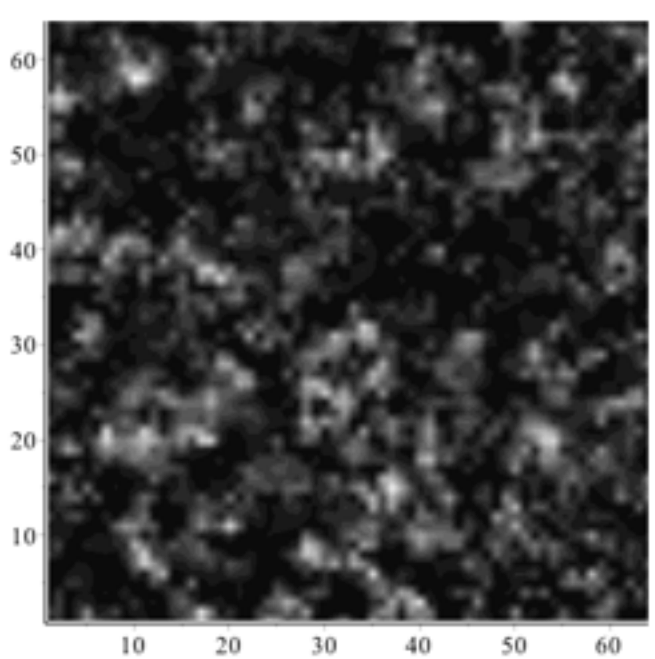


The waves size decreases hyperbolically with the strength of sAHP

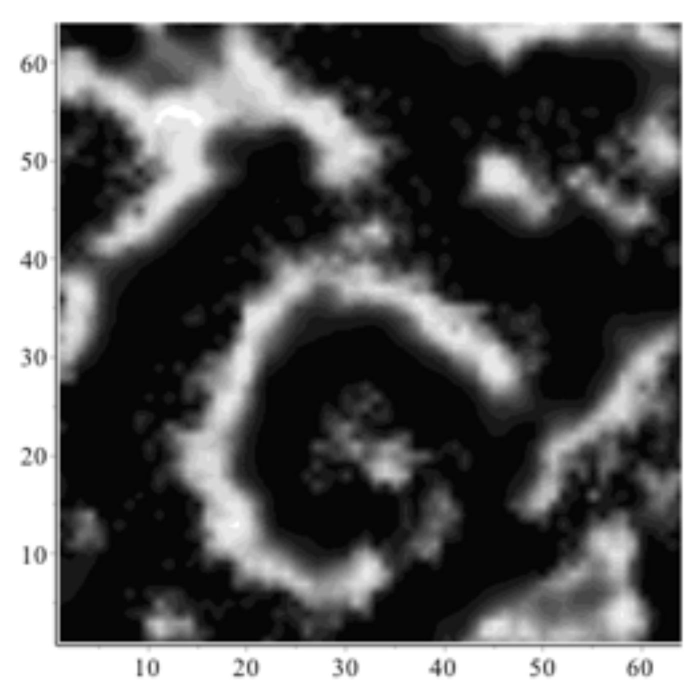
Patterns evolve within stage II



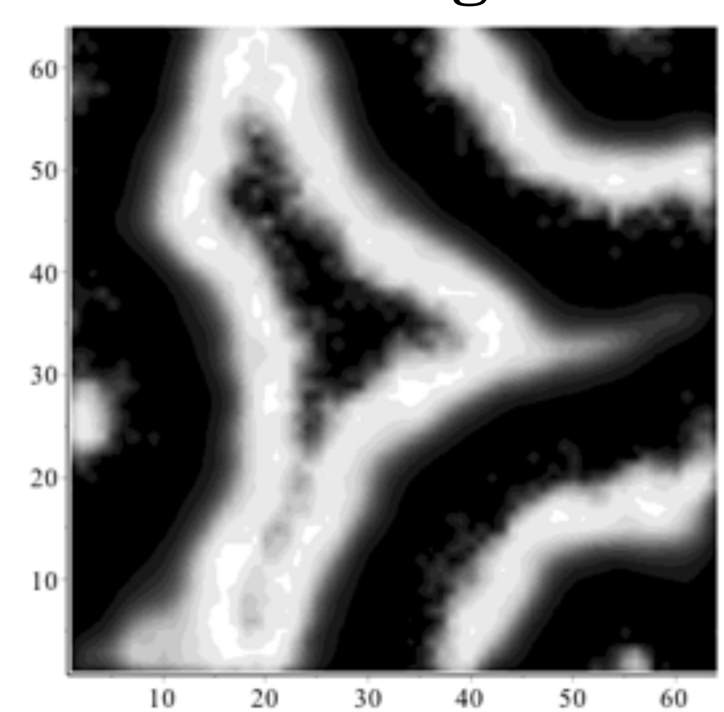
Weak



Moderate



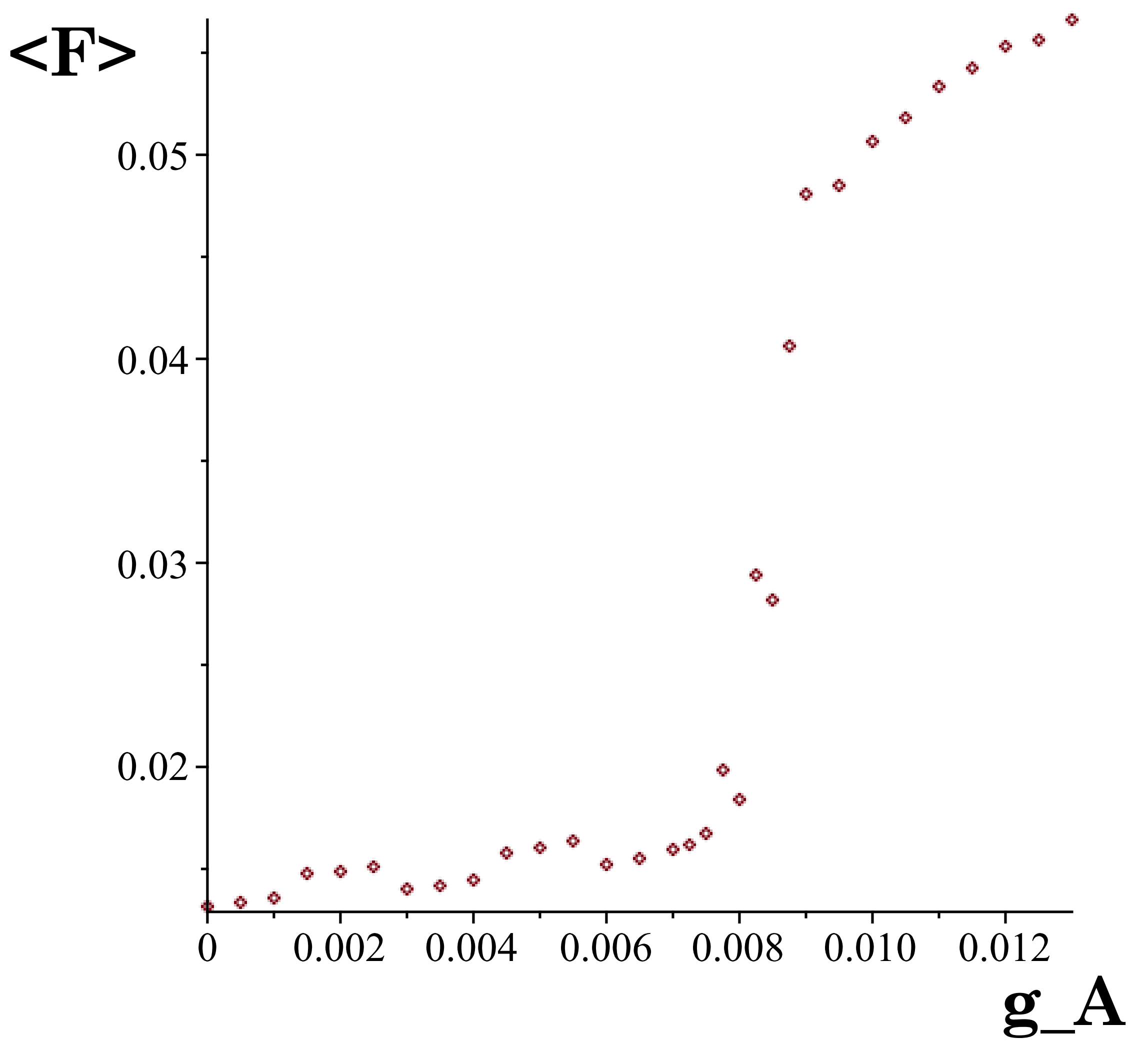
Strong



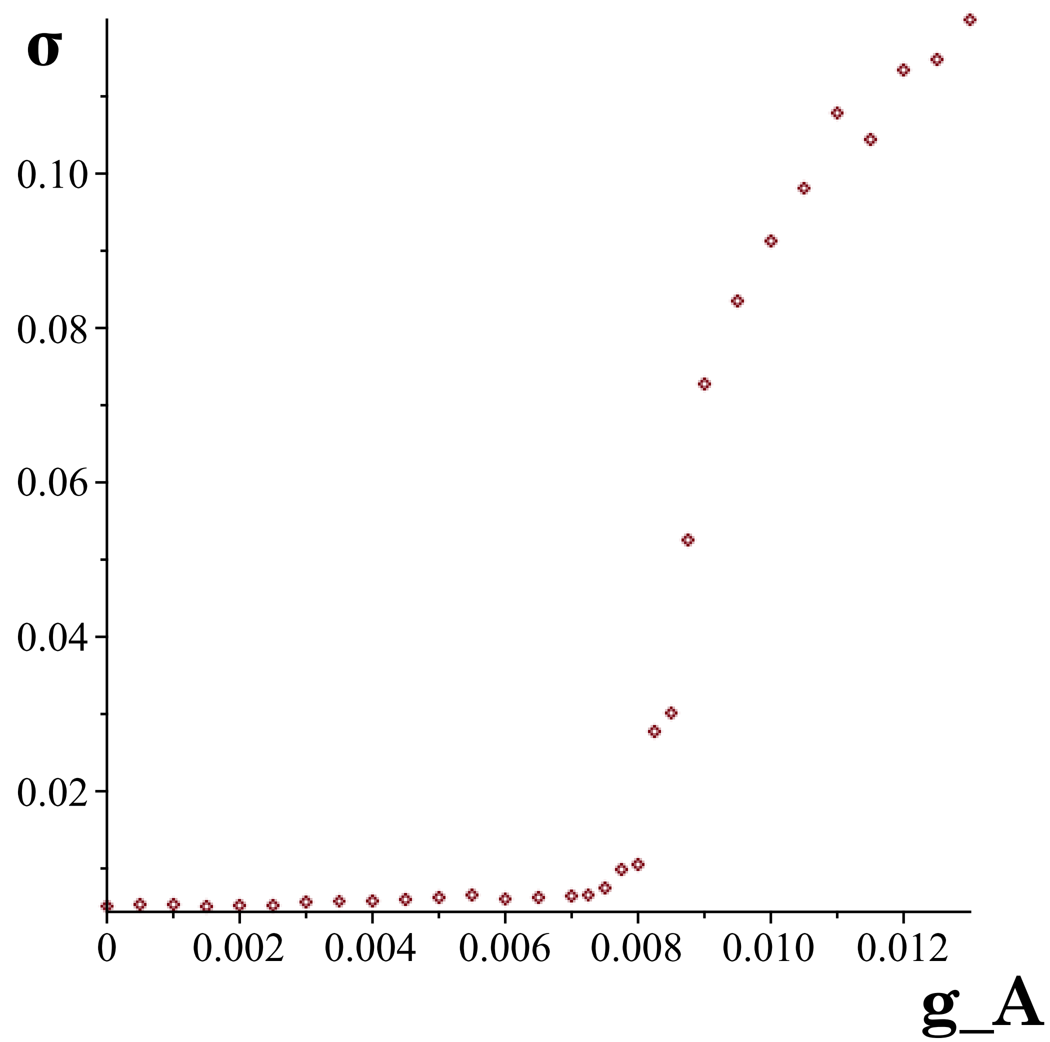
gA (nS)

Synchronisation Transition

Average population firing rate



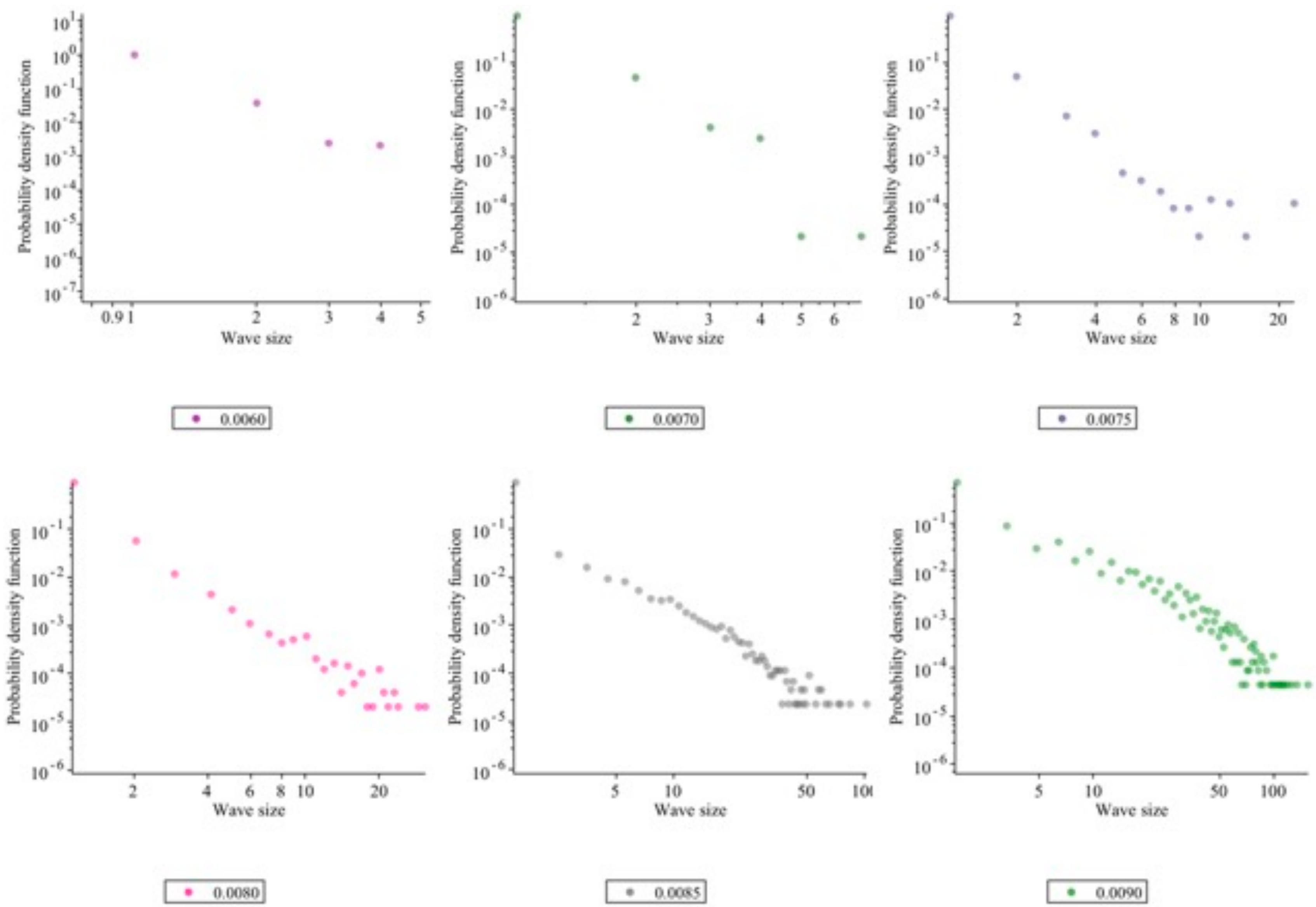
Standard deviation firing rate



The average and the std of the population firing rate undergo a transition at a specific range of cholinergic coupling

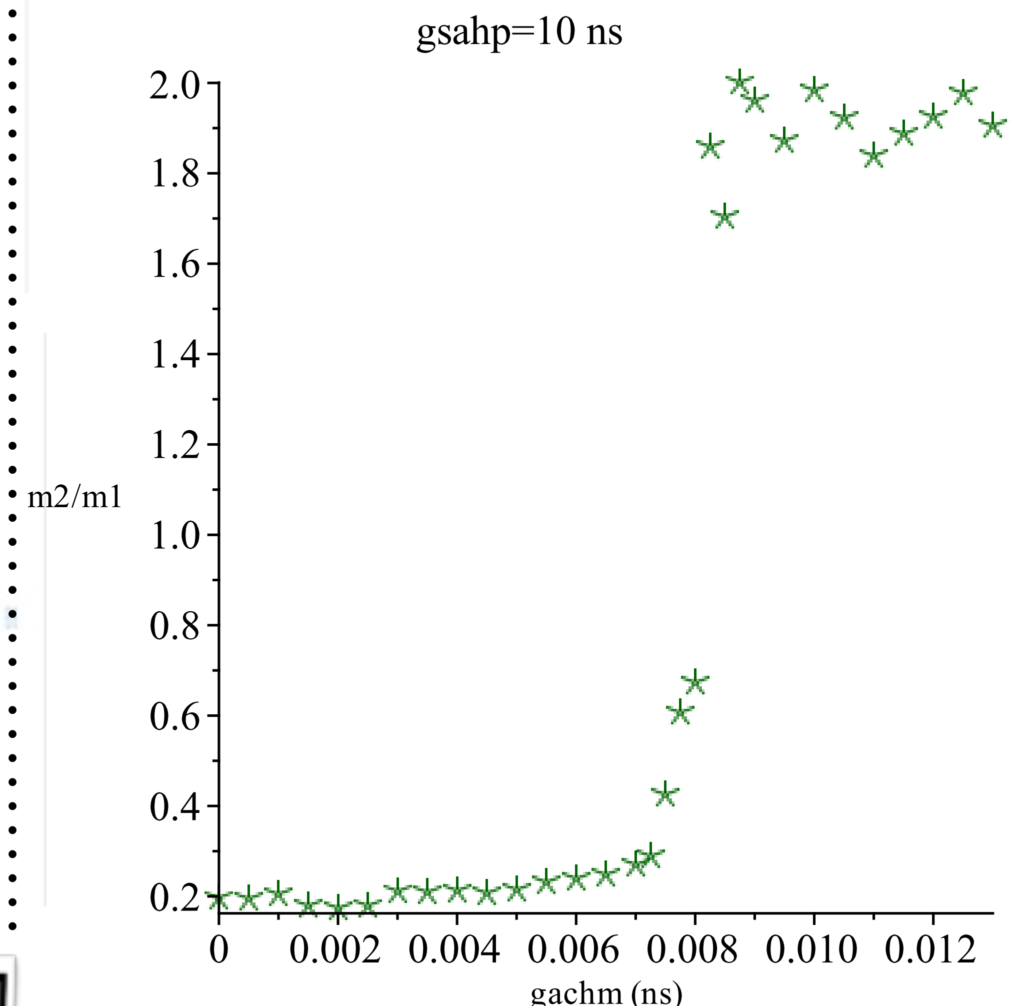
Synchronisation Transition

Distribution of waves sizes



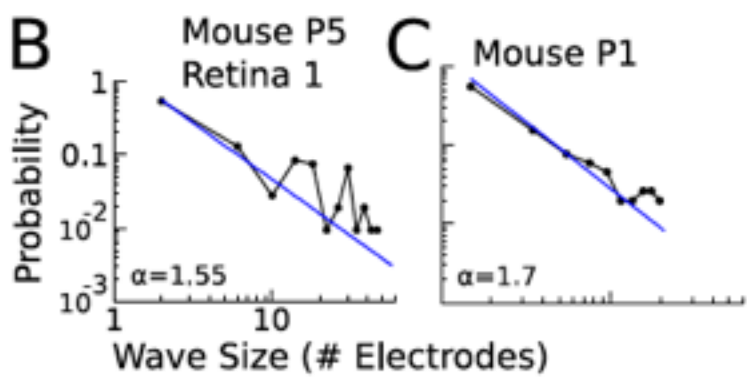
Fano coefficient

Ratio of mean and standard deviation of a distribution



Our model indicates the existence of power law like distributions for waves sizes for a range of coupling strength

Indications for criticality in experiments



Hennig et al. 2009

- Hennig et. al 2009 also found **power law -like distributions** for the waves sizes
- Criticality is a precise concept in physics and **power law distributions are not enough** to characterise it
- Also, criticality is not a natural state and it is achieved by **bringing the system to a specific point**

Two "critical" points:
i) **Experimental data** need to be analysed in a **more elaborate way** to reveal the actual distributions of waves characteristics
ii) If indeed there is criticality and power laws, then we miss a **mechanism that brings the system to the critical point**

Conclusions & Perspectives

- **Analysing** the dynamics of our model using **dynamical systems theory** leading to a main hypothesis: **Immature SACs are near a bifurcation point!**
- **Consequences:**
    - **individual SACs properties***
    - **how SACs lose their excitability upon maturation**
    - **explain variability of wave features across species**
    - **wave propagation conditions***
    - **criticality and power laws***
    - **spontaneous activity could be generated by a SACs network that is optimised for input processing=dynamic range**
- **Future direction towards completing studying waves in a dynamically changing landscape**
- **Characterise criticality in our model and use the same tools to characterise experimental data**

- **Proposing new experiments** based on theoretical hypothesis

Thank you all

:)